FORMULATION AND EVALUATION OF FLOATING CONTROLLED RELEASE TABLETS OF CARVEDILOL BY USING NATURAL POLYMERS

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IN

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Submitted by

Reg. No. 26103011

Under the guidance of

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Komarapalayam – 638 183

Tamil Nadu

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Certificates

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF FLOATING CONTROLLED RELEASE TABLETS OF CARVEDILOL BY USING NATURAL POLYMERS"** submitted by the student bearing **Reg. No. 26103011** to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on…….

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"FORMULATION AND EVALUATION OF FLOATING CONTROLLED RELEASE TABLETS OF CARVEDILOL BY USING NATURAL POLYMERS",** submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai, was carried out by **RENUKA UPPUTURI, [REG.NO: 26103011],** for the partial fulfillment of Degree of **MASTER OF PHARMACY** in Pharmaceutics under direct supervision of **Mrs. S. BHAMA, M.Pharm.,** Assistant Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Komarapalayam, during the academic year 2011-2012.

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DECLARATION

The work presented in this dissertation entitled **"FORMULATION AND EVALUATION OF FLOATING CONTROLLED RELEASE TABLETS OF CARVEDILOL BY USING NATURAL POLYMERS",** was carried out by me, under the direct supervision of **Mrs. S. BHAMA, M.Pharm.,** Assistant professor, Department of pharmaceutics, J.K.K. Nattraja College of Pharmacy, Komarapalayam.

I further declare that, this work is original and has not been submitted in part or full for the award of any other degree or diploma in any other university.

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RENUKA.UPPUTURI,

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Dedicated to
Almighty
My Beloved family members
and my friend

Contents

CONTENTS

LIST OF ABBREVIATIONS USED

BLT	-	Buoyancy lag time
CR	-	Controlled release
DDS	-	Drug delivery system
DI	-	Dosage form index
MED	-	Median effective dose
FT-IR	-	Fourier transform infra red
GIT	-	Gastro intestinal tract
HPMC	-	Hydroxy propyl methyl cellulose
ICH	-	International conference of Hormonisation
MEC	-	Minimum effective concentration
MTC	-	Maximum therapeutic concentration
PA	-	Prolonged release
SA	-	Sustained action
SR	-	Sustained release
MTD	-	Medicine toxic dose
CP	-	Carvedilol phosphate
PPHCL	-	Propranolal hydrochloride
TFT	-	Total floating time
GRDF	-	Gastroretentive dosage forms
MMC	-	Myloelectric cycle
GRT	-	Gastric retention time
FDDS	-	Floating drug delivery system
HBS	-	Hydrodynamically balanced system

Chapter I

Introduction

1. INTRODUCTION

1.1 ORAL CONTROLLED DRUG DELIVERY SYSTEM

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process[1].

Pharmaceutical products were designed for oral delivery are mainly conventional drug delivery systems, which given immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as[2, 3]:

1) Drugs with short half-life require frequent administration, which increase the chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{SS} values fall or rise beyond the therapeutic range.

4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits[4].

1.2 Controlled Drug Delivery Systems:

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue[5].

Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1) Delayed release

2) Sustained release

3) Site-specific targeting

4) Receptor targeting

More precisely, Controlled delivery can be defined as[6]: -

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.

2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.

3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.

4) Provide a physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in

substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

1.3 Advantages of Controlled Drug Delivery System[6]:

1. Avoid patient compliance problems.
2. Minimization of dosing frequency.
3. Minimize or eliminate local/systemic side effects.
4. Minimize drug accumulation with chronic dosing.
5. To obtain better therapeutic efficacy and diminished toxicity.
6. Increased safety margin of high potency drugs due to control of plasma levels.
7. Maximum utilization of drug enabling reduction in total amount of dose administered.
8. Reductions in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administers and monitor the patients.

1.4 Disadvantages[7]:

1) Decreased systemic availability in comparison to conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.

2) Poor *in vitro – in vivo* correlation.

3) Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.

4) Retrievals of drug are difficult in case of toxicity, poisoning or hypersensitivity reactions.

5) Reduced potential for dosage adjustment of drugs normally administered in varying strengths.

1.5 Oral Controlled Drug Delivery Systems[8]:

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

The main areas of potential challenge in the development of oral controlled drug delivery systems are[9]: -

1) Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.

2) Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.

3) Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

Conventional oral controlled dosage forms suffer from mainly two adversities[10]. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms.

Altering the gastric emptying can overwhelm these problems. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time.

Extended release dosage form with prolonged residence time in stomach are highly desirable for drugs[11,12.].

- That are locally active in stomach.
- That have an absorption window in the stomach or in the upper small intestine.
- That are unstable in the intestinal or colonic environment.
- Have low solubility at high pH values.

1.6 Gastro-retentive dosage forms (GRDF)[13,14]:

These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug

for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs.

The gastric emptying time mainly depends upon the design of the dosage form and physiological state of the subject, which last from a few minutes to 12hrs. The average gastric emptying time in human is 2-3hrs through major absorption zone (stomach and upper part of the intestine), which leads to incomplete drug release from the DDS leading to diminished efficacy of the administered dose. So drugs which have stability problem, GRDF plays an important role. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilitie.

GRDF will also greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time[15].

Finally, GRDF will be used as carriers for drugs with so called absorption windows: these substances are taken up only from very specific sites of the gastrointestinal mucosa, often in a proximal region of the small intestine. Need of gastro retention arises because of two reasons, viz .

I. To improve bioavailability of drugs such as cyclosporin, ciprofloxacin, ranitidine, metoprolol tartarate, cefuroxime axetil etc. which are mainly absorbed from upper part of GIT or get degraded in alkaline P^H.

II. For local action in case of pathologies of stomach.

1.7 BIOLOGICAL ASPECTS OF GRDFS (FIG. 1):

a) Role of GI Tract[16,17] : stomach

The stomach is j- shaped organ located in the upper left hand portion of the abdomen just below the diaphragm. It occupies a portion of the epigastric and left hypochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach.

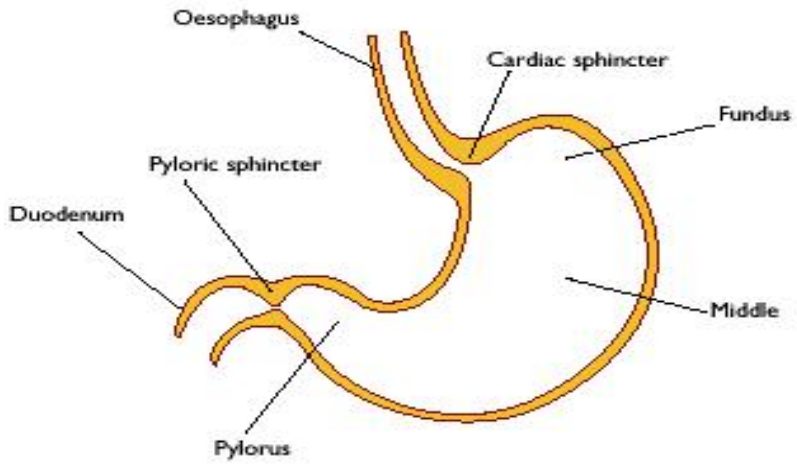


Fig No. 1: Anatomy of the stomach.

The stomach has four main regions:

1. Cardia
2. Fundus
3. Body and
4. Pylorus

The main function of the fundus and body is storage, whereas that of cardia is mixing or grinding. The fundus adjusts the increased volume during eating by relaxation of the fundus muscle fibers. The fundus also exerts a steady pressure on the gastric contents pressing them towards the distal region, to pass through the pyloric sphincter into the small intestine.

Gastric motility:

Gastric emptying occurs during fasting as well as fed states. During the fasting state an interdigestive series of electrical events take place, which cycles through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into 4 phases as described by Wilson and Washington.

1. Phase I (basal phase): period of no contraction.

2. Phase II (preburst phase): period of intermittent contraction.

3. Phase III (burst phase) : period of regular contractions at the maximal frequency that migrate distally.[17,18]

4. Phase IV : period of transition b/w phase III and phase I.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. It can be concluded that feeding results in a lag time before onset of gastric emptying cycle.

Gastrointestinal Transit Time:

Food content remains in each segment of the gastrointestinal tract for different periods of time.

Table No.1: Transit time of food in each segment of the gastrointestinal tract

Segment	*Liquid*	*Solid*
Stomach	10-30min	1-3 hours
Duodenum	<60sec	<60 sec
Jejunum and ileum	3 hours ± 1.5 hours	4 hours ± 1.5 hours
Colon	----------	20-50 hours

Since most of the drugs are absorbed from the upper part of intestine, the total effective time for the drug absorption is 3-8 hours. So one has to take most of the drugs 3-6 times a day.

c) Various factors affecting the gastric emptying time[18]:

I. State of the stomach: gastric emptying time depends upon the fed state of the stomach, which increases the gastric emptying time as compared to unfed state.

II. Circadian rhythms: which are increased in daytime and less during night, also affects the gastric retention time (GRT).

III. Size of the dosage form: greater the energy content of the meal (carbohydrate and high fat content), longer the duration of emptying.

IV. Density of the oral dosage form: The density of the gastric fluid is reported to be 1.2g/cm^3. The density of the dosage form should be less than this for the buoyancy so that it is retained in the stomach for longer period of time.

V. Diseased state: State of the stomach also affects the environment for the dosage form as in case of ulcers, flatulence and spasms.

VI. Drug therapy: Plays an important role in gastric emptying e.g. prokinetic drugs like cisapride and mosapride increase the gastric emptying time.

VII. Age: Increase in age decreases the gastric motility thereby increasing the gastric emptying time.

VIII. Posture: It was seen that the supine posture on the right side showed better results than on the left side.

d) Criteria for selection of drug candidate for GRDF[19] :

The gastric retentive drug delivery systems are suitable for following types of drug therapy:

I. Absorption from upper GIT: Drugs have a particular site for maximum absorption e.g. ciprofloxacin, whose maximum absorption is in the stomach only. The absorption of metformin hydrochloride is confirmed to small intestine only and the conventional sustained release dosage forms may be poorly bioavailable since absorption appears to diminish when the dosage form pass in to large intestine.

II. Drugs having low P^{Ka}, which remains unionized in stomach for better absorption.

III. Drugs having reduced solubility at higher P^{H} e.g. captopril and chlordiazepoxide and the bioavailability of drugs that get degraded in alkaline P^{H} can be increased by formulating gastro-retentive dosage forms. e.g. doxifluridine, which degrades in small intestine.

IV. Local action as it is seen in the treatment of *H. Pylori* by amoxicillin and misoprostol for ulcers.

V. To minimize gastric irritation which may be caused by sudden increase of drug concentration in the stomach. e.g. NSAIDs.

VI. Improve effectiveness of particular drugs. E.g. antibiotics in the colon tend to disturb the microflora causing overgrowth of microorganisms like Clostridium difficile causing colitis.

GASTRO RETENTIVE DRUG DELIVERY SYSTEM:

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. Oral medication is generally considered as the first avenue investigated in the development of pharmaceutical formulations because of patient acceptance, convenience in administration and cost effective manufacturing processes. Oral route offers an attractive approach of drug targeting at the specific site within GI tract for certain types of drug.

1.8 Approaches to Gastric Retention[20] :

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include:

a) Floating Systems[21]:

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, effervescent and non-effervescent systems

b) Bio/Muco-adhesive Systems[22] :

Bio/Muco-adhesive systems are those which bind to the gastric epithelial surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI

wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect. Binding of polymers to the mucin/epithelial surface can be divided into three broad categories:

1. Hydration-mediated adhesion.
2. Bonding-mediated adhesion.
3. Receptor-mediated adhesion.

c) Swelling and Expanding Systems[23] :

These are the dosage forms, which after swallowing, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer. These systems may be named as “plug type system” since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state.

A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability and maintains its physical integrity for prolonged period.

d) High Density Systems[24]:

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which systems can be retained in the lower part of the stomach. High-density formulations include coated pellets.

Coating is done by heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, and iron powder.

e) Incorporation of Passage Delaying Food Agents:

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}-C_{14}.

f) Ion Exchange Resins[25]:

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place, as a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

g) Osmotic Regulated Systems[26]:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components, drug reservoir compartment and osmotically active compartment.

1.9 Types of Floating Drug Delivery Systems (FDDS)[27,28]:

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS, which are:

A. **Effervescent System**

B. **Non- Effervescent System**

A) EFFERVESCENT SYSTEMS:

Effervescent systems include use of gas generating agents, carbonates (sodium bicarbonate) and other organic acid (citric acid and tartaric acid) to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it to float on the gastric fluid. These effervescent systems further classified into two types.

I. Gas generating systems:

1. **Intra Gastric Single Layer Floating Tablet or Hydrodynamically Balanced System (HBS**)

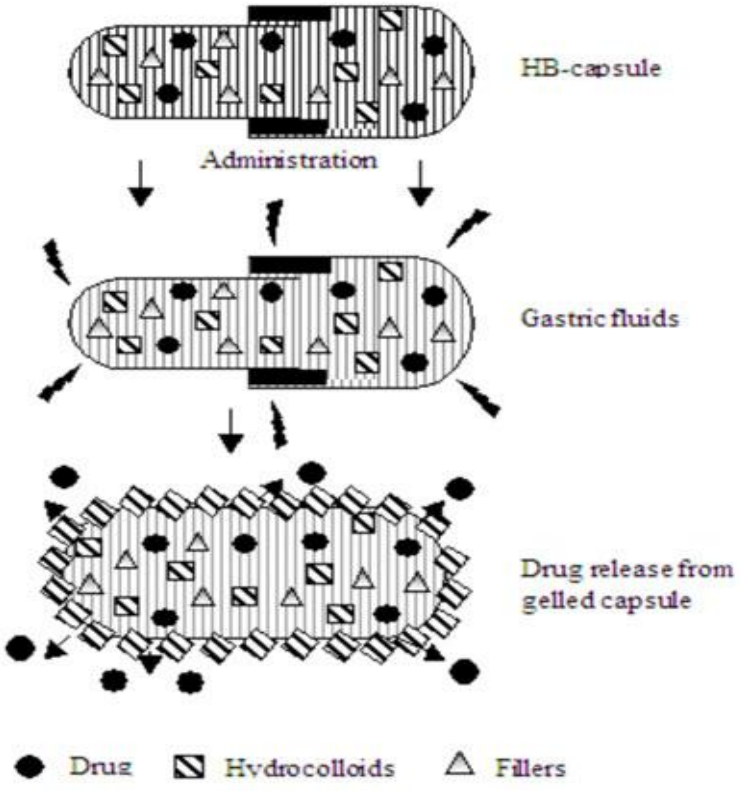


Fig No. 2: hydrodynamically balanced system

These are formulated by mixing the CO_2 generating agents and the drug with in the matrix tablet (Fig. 2). These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

2. Intra Gastric Bilayered Floating Tablets:

These are also compressed tablet and contains two layers for:

i) Immediate release layer and ii) Sustained release layer (Fig. 3).

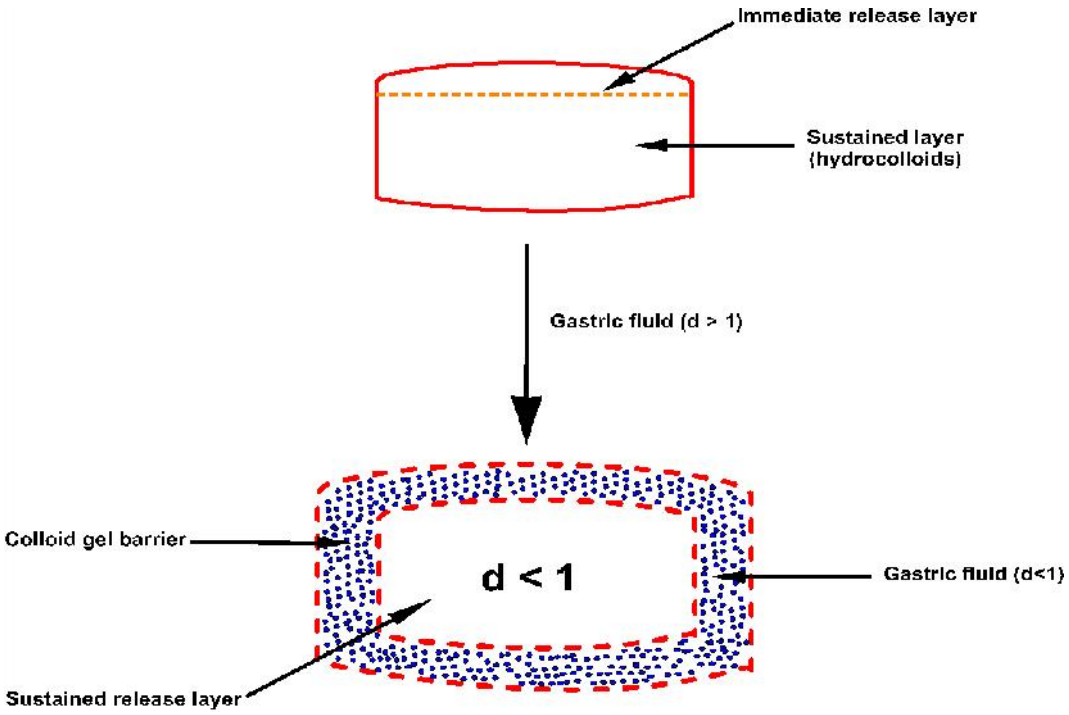


Fig No. 3: Intra Gastric Bilayer Floating Tablet.

3. Multiple Unit type floating pills:

These systems consist of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium

at body temperature it sinks at once and then forms swollen pill like balloon and float as the density decreases (Fig. 4&5).

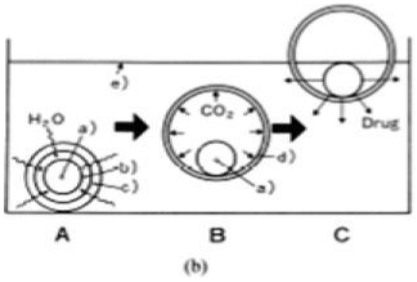


Fig No.4: Stages of floating mechanism

A.Penetration of water

B.Generation of CO_2 and floating

C. Dissolution of drug

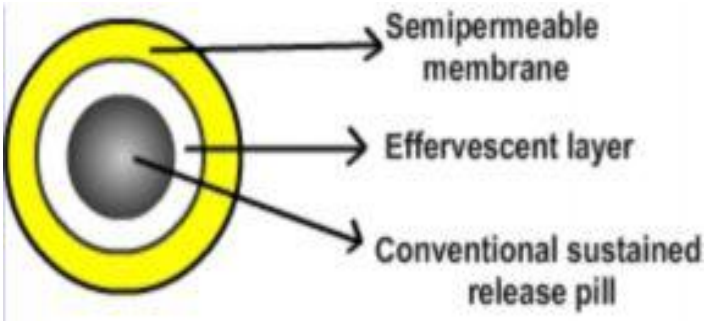


Fig No.5: A multi-unit type oral floating dosage system

II. Volatile Liquid / Vacuum Containing Systems[29]:

1. Intragastric Floating Gastrointestinal Drug Delivery System:

These system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporus compartment (Fig. 6).

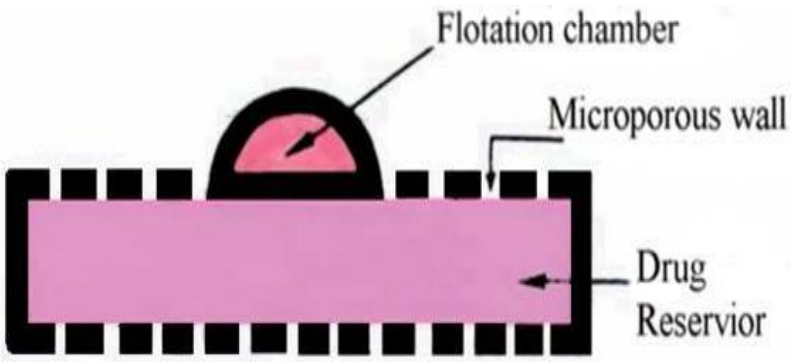


Fig No. 6: Intra Gastric Floating Gastrointestinal Drug Delivery Device

2. Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid (Fig. 7).

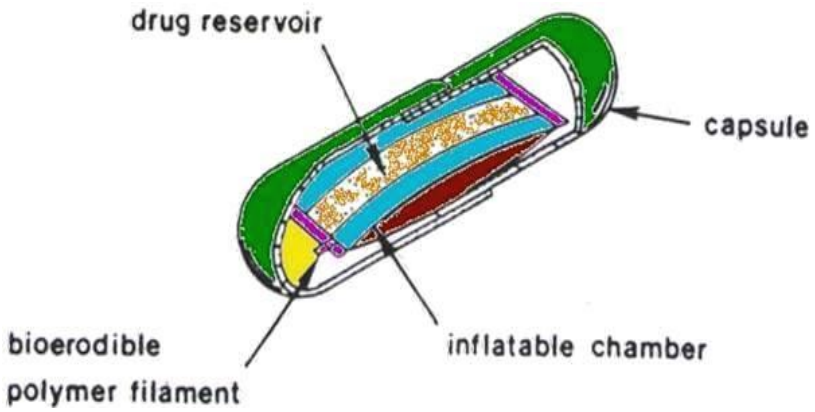


Fig No. 7: Inflatable Gastrointestinal Delivery System

3. Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach capsule

quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and turns in forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release in solution form through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach (Fig. 8).

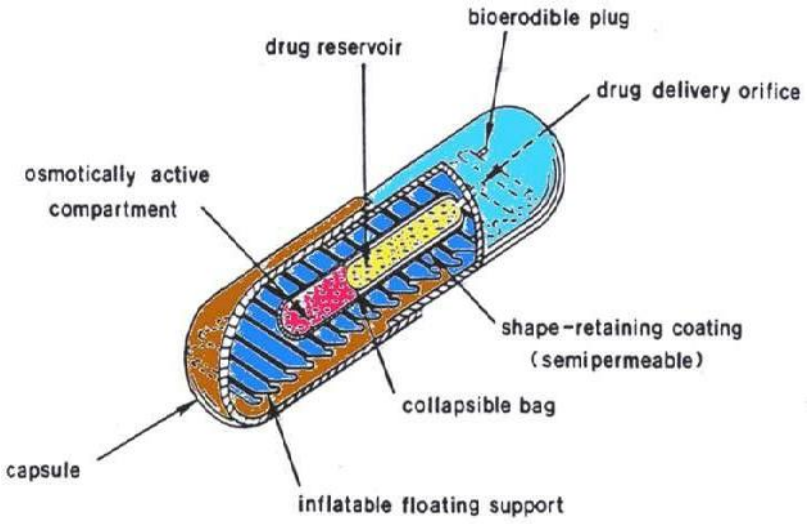


Fig No. 8: Intragastric Osmotically Controlled Drug Delivery System

B) Non Effeverscent systems[30];

The Non effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials such as polycarbonates, polyacrylates, polymethacrylates, polystyrenes etc. and bioadhesive polymer such as chitosan and carbopol.

The various types of these systems are:

1. Single Layer Floating Tablets:

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2. Alginate Beads:

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hour.

3. Hollow Microspheres:

Multiple-unit hollow microspheres by emulsion solvent diffusion technique were prepared with Drug and acrylic polymer. These were dissolved in an ethanol-dichloromethane mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer to drug ratio. Microballoons were floatable in vitro for 12 hours when immersed in aqueous media. Radiographical studies proved that

microballoons orally administered to humans were dispersed in the upper part of stomach and retained there for 3 hours against peristaltic movements.

Advantages of FDDS[31,32]:

1. Drugs that act locally in the stomach e.g., Antacids, Antibiotics for microbial based ulcers, etc.

2. Drugs that are absorbed primarily in the stomach e.g., Albuterol.

3. Drugs that are poorly soluble in alkaline pH.

4. Drugs that have a narrow window for absorption. i.e., Drugs that are absorbed mainly from the proximal part of small intestine. e.g., Riboflavin, Levodopa, p-amino benzoic acid.

5. Drugs that are absorbed rapidly from the GI tract. e.g., Amoxicillin.

6. Drugs that degrade in the colon. e.g., Captopril, Metoprolol.

Disadvantages of FDDS:

1. High Variability in gastric emptying time due to variations in emptying process.

2. Drugs that cause irritation and lesions to gastric mucosa and unstable in gastric fluid cannot be formulated as FDDS.

3. Drug with unpredictable bioavailability, minimum effective concentration is achieved slowly.

4. Gastric retention is influenced by many factors such as gastric motility, pH, and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.

Application of FDDS:

1. For treating local inflammation and stomach ulcers.

2. For treating *H. Pylori* associated ulcers.

3. In chronic diseases associated with frequent medication and prolonged medication, FDDS can be promising drug delivery.

HYPERTENSION

Cardiovascular diseases are one of the life threatening diseases of mankind and hypertension is the most common cardiovascular disease, which requires constant monitoring. It is well known that hypertension is a major factor for congestive cardiac failure and coronary artery disease.

Hypertension or high blood pressure is a condition in which the blood pressure in the arteries is chronically elevated. With every heart beat, the heart pumps blood through the arteries to the rest of the body. Blood pressure is the force of blood that is pushing up against the walls of the blood vessels. If the pressure is too high, the heart has to work harder to pump, and this could lead to organ damage and several illnesses such as heart attack, stroke, heart failure, aneurysm, or renal failure.

The current definition (WHO, 1996) of hypertension is level of systolic blood pressure of 140 mm Hg or above, a level of diastolic pressure of 90 mm Hg or above, by repeated measurement over periods of several weeks. It may be systolic or diastolic, diastolic hypertension when diastolic BP is found to be 90 mm Hg or more on two consecutive visits[33].

Classification of hypertension:

Hypertension is classified as either primary (essential) hypertension or secondary hypertension.

About 90-95% of cases are categorized as “primary hypertension” which means high blood pressure with no obvious medical cause[34].

The remaining 5-10 % of cases (secondary hypertension) are caused by other conditions that affect the kidneys,arteries,heart or endrocrine system.

Persistent hypertension is a major risk factor for stroke, myocardial infarction (heart attacks), heart failure and aneurysms of the arteries (e.g. aortic aneurysm), and is a cause of chronic kidney disease. Even moderate elevation of arterial blood

pressure is associated with a shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications, although drug treatment is often necessary in patients for whom lifestyle changes prove ineffective or insufficient.

Table No.2: classification of hypertension

Category	Systolic (mm of Hg)	Diastolic (mm of Hg)
Normal	>130	<85
High Normal	130-139	85-89
Hypertension		
Mild stage (stage 1)	140-159	90-99
Moderate (stage 2)	160-179	100-109
Severe (stage 3)	180-209	110-119
Very sever (stage 4)	>210	>120
Malignant hypertension	>200	>140

Etiology:

In the year 2000 it is estimated that nearly one billion people or ~26% of the adult population had hypertension worldwide[35]. It was common in both developed (333 million) and undeveloped (639 million) countries. However rates vary markedly in different regions with rates as low as 3.4% (men) and 6.8% (women) in rural India and as high as 68.9% (men) and 72.5% (women) in Poland.

In 1995 it is estimated that 43 million people in the United States had hypertension or were taking antihypertensive medication, almost 24% of the adult population[36]. The prevalence of hypertension in the United States is increasing and

reached 29% in 2004.It is more common in blacks and native Americans and less in whites and Mexican Americans, rates increase with age, and is greater in the southeastern United States. Hypertension is more prevalent in men (though menopause tends to decrease this difference) and those of low socioeconomic status.

Over 90–95% of adult hypertension is essential hypertension. One of the most common causes of secondary hypertension is primary aldosteronism[37].

Antihypertensive agents:

Antihypertensive agents are the drugs which lower the blood pressure in hypertensive patients.

a. Classification of antihypertensives:

1. Diuretics

   eg. Chlorthalidone, Clopamide, Indapamide

2. β Adrenergic blockers

   eg.Acebutolol, Atenolol, Metoprolol, Propranolol, Timolol

3. α Adrenergic blockers

   eg. Terazosin, Prazosin, Doxazosin

4. α + β Adrenergic blockers

   eg. Labetalol, Carvedilol

5. ACE inhibitors

   eg. Perindopril, Captopril, Enalapril, Lisinopril, Fosinopril, trandolapril, benazepril etc.

6. Calcium channel blockers

eg. Amlodipine, Felodipine Nifedipine, Nimodipine, Verapamil

7. Vasodilators

eg. Hydralazine, Minoxidil, Sodium nitroprusside

8. Angiotension-II receptor antagonists

eg. Candesartan, Losartan, Valsartan

9. Central sympatholytics

eg. Clonidine, Methyldopa

Chapter II

Literature Review

2. LITERATURE REVIEW

Vaidya M.P et.al., [38] prepared a floating gastroretentive sustained release drug delivery system of Carvedilol phosphate (CP) wherein the tablet floats on the gastric fluids and sustains the release of drug for prolonged period of time. Carvedilol phosphate is a poorly water-soluble, beta-adrenergic receptor blocking agent with ancillary vasodilatory properties, with problems like variable bioavailability and bio-inequivalence which can be related to its poor solubility. CP exhibits typical solubility behavior in neutral or alkaline media, the solubility of CP is maximum in the upper part of gastrointestinal tract. The floating gastroretentive sustained release drug delivery system was prepared by using gas generating agent like sodium bicarbonate and release retardant polymer HPMC by direct compression method. HPLC and UV spectrophotometric analytical methods were developed for estimation of CP from formulations. The tablets were prepared and optimized by using 32 full factorial design.The tablets were evaluated for hardness, friability, weight variation, drug content, buoyancy lag time, buoyancy time, swelling index, erosion study and in-vitro dissolution profile. The drug release rate from CP floating gastroretentive sustained release tablet was sustained up to 12 hr i.e. 93.62% by incorporation of HPMC-K100M and sodium bicarbonate in the concentration of 46.66% and 19% respectively, which caused the floating of tablet within 8 sec .The current study attained the successful design, preparation and evaluation of floating sustained release formulation of a poorly soluble drug CP by gastroretentive drug delivery system, which sustained the release profile and achieved gastric retention for the desired period of time.

ML Varahala Setti et al.,[39] reported a controlled release tablets of carvedilol, employing synthetic polymers like polyethylene oxides, of different molecular weights as release retarding materials and to select the optimized formulation based on the pharmacokinetics of carvedilol. Matrix tablets each containing 80 mg of carvedilol were formulated employing PEO N60 K,PEO 301, and PEO 303 as release retarding polymers and β cyclodextirin and HP β cyclodextrin as release modulators from the matrix. Carvedilol release from the formulated tablets was very

slow. Hence the release was modulated with the use of cyclodextrins. The dissolution from the matrix tablets was spread over more than 24 hrs and depended on the type of polymer, its concentration and the type of cyclodextrin used. All the matrix tablets prepared using HP β cyclodextrin showed a higher dissoluition rate and gave a dissolution profile that was comparable to the theoretical sustained release needed for once-a-day administration of carvedilol. The drug release mechanism from the matrix tablets was found to be quasi fickian mechanism.

M. P. Venkatarajua et.al.,[40] developed a controlled delivery system for propranolol hydrochloride (PPHCL) using the synergistic activity of locust bean gum (LBG) and xanthan gum (X). Granules of PPHCL were prepared by using different drug: gum ratios of X, LBG alone and a mixture of XLBG (X and LBG in 1: 1 ratios). To increase the flowability and compressibility of the granules, and to prevent its adhesion to the punch and die, magnesium stearate (Mg. st) and talc were added to the granules in a 1: 2 ratio before punching. The tablets were analysed to determine their hardness, friability, and composition% and an *in vitro* release study was carried out. The release of PPHCL from a gelatinous swollen mass controlled the diffusion of drug molecules through the polymeric material into aqueous medium. The XLBG matrices exhibited precise controlled release than the X and LBG matrices because of burst effect and fast release in case of X and LBG alone respectively and there was no chemical interaction between drug and polymers in the XLBG formulation as confirmed by FTIR studies. The first-pass effect of PPHCL can be avoided by using this formulation. The XLBG matrices offer more precise results than X and LBG matrices due to the effect of a synergistic interaction between the two biopolymers and the lower average size allowing uniform tablet hydration in dissolution media.

Parikh Bhavik Anjankumar et.al.,[41] prepared a floating Drug delivery system of Atenolol in order to increase the gastric residence time (GRT) and comparison of natural and synthetic polymer for better sustained effect. The tablets were prepared by direct compression. The pre and post compression studies were performed by using IP standard formula and procedure. Drug release from the floating drug delivery system was studied using USP II .The

release behavior of the natural and synthetic polymer was compared according to obtained data. The hardness of all formulations was found to be in the range of 3.5- 4.0 kg/cm2. Among all these formulations (A1 to A4) prepared by direct compression, batch A4 was selected as best formulation and showed very slow release i.e. 52.67% in 12 hr. The drug release of the other formulation like A1 to A3 (96.56%, 81.83%, 69.23% in 12h).It was higher from the F1 formulation prepared by direct compression. Natural polymer showed better sustained release properties than synthetic polymer. The formulation with guar gum and xanthum gum showed better sustained release effect than HPMC different grade. The developed floating tablets of Atenolol may be used in clinic for prolonged drug release for at least 12hrs, thereby improving the bioavailability and patient compliance.

Honglei Jian et.al.,[42] developed a controlled release tablets of theophylline using sustained release materials such as Galactomannan (G) from Gleditsia sinensis Lam. and xanthan gum (X), were mixed indifferent ratios of 7: 3, 5:5 , and 3:7 to yield enhanced release-controlling performance. The polysaccharides content of tablets was 10% (w/w), either alone or in mixtures. From *in vitro* dissolution test, G10% and X10% matrices released 91.4 and 87.7% of Drug within 24 hrs, respectively. The synergistic interactions between galactomanna and xanthan effectively retarded the drug diffusion , and the most sustained drug release (75% at 24 hr) was found in formulation GX7:3. The drug release data fitted to the Kinetic model indicated the anomalous transport mechanism ($0.5 < n < 1.0$). Additionally, The swelling behavior and morphological changes of the tablets were investigated. The Results illustrated the potential of binary mixtures of G.sinensis galactomannan and xanthan as novel sustained release materials for controlled drug delivery.

Dale L. Mundan et.al.,[43] were produced directly compressed matrices containing either xanthan gum or karaya gum as a release-controlling agent. Xanthan gum displayed a high degree of swelling due to water uptake and a small Degree of erosion due to polymer relaxation . Neither agitation speed nor drug solubility had any significant effect on water uptake, but matrices with the

lower proportion of gum produced a lesser degree of hydration. In contrast, karaya gum displayed a much lower hydration capacity and a higher rate of erosion, both markedly affected by agitation speed. Drug release from xanthan and karaya gum matrices depended on agitation speed, solubility and proportion of drug. Both xanthan and karya gums produced near zero order drug release with the erosion mechanism playing a dominant role, especially in karaya gum matrices.

T. Akelesh,et al.,[44] developed a gastro-retentive floating tablet Of Acyclovir by direct compression method.The results of *in vitro* release studies showed that optimized formulation F7 Could Sustain drug release (99.08%) for 16 hr and remain buoyant for 24 hrs . Optimized formulation F7 Contained 60% of Locust bean gum and 40% Sodium alginate out of total floating polymer while Amount of Xanthan gum is same in all 7 batches . F7 formulation fitted best for koresmeyer- Peppas model and showed no change in physical appearance, drug content, friability or *Invitro* dissolution pattern after storage at 45 ^{o}c /75% RH for two months .

Mahesh Chavanpatil.et.al.,[45] developed ofloxacin Sustained release (SR)-gastroretentive dosage forms (GRDF) for once daily. The design of the delivery system was based on the sustained release formulation, with floating and swelling features in order to prolong the gastric retention time of the drug delivery systems. Different polymers, such as psyllium husk, HPMC K100M,crospovidone and its combinations were tried in order to get the desired sustained release profile over a period of 24 hr. It was found that dimensional stability of the formulation increaseed with the increasing psyllium husk concentration. It was also found that in vitro drug release rate increased with increasing amount of Crospovidone due to the increased water uptake , and hence increased driving force for drug release. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. In vivo studies were carried out for the optimized formulation in 24 healthy human volunteers and the pharmaco-kinetic parameters of developed formulations were compared with the marketed

once daily (Zanocin) formulation. Based on the in vivo performance in a parallel study design in healthy subjects, the developed formulation showed promise to be bioequivalent to the marketed product (Zanocin). The percent relative bioavailability of developed formulation was found to be 97.55%.

Raja Sekharan T, et.al.,[46] prepared Theophylline controlled release matrix tablets with Guar Gum in two ratios and with three different hardness of 5, 6 and 7kg/cm2. Theophylline Controlled release granules were prepared and evaluated for the angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. All the formulation showed good flow properties. The compressed tablets were evaluated for the hardness, uniformity of weight, friability , drug content and invitro dissolution studies. All the formulations showed compliance with pharmacoepial standards. There was no interaction between drug, polymer and other excipients. It was confirmed by FTIR studies. Among all the formulations F6 (i.e. polymer ratio1:2 and hardness 7kg/cm2) showed prolong release when compare to other formulations. The drug release kinetics showed zero order. The optimum formulation (F6 was stable when it was stored at 40 ^{o}c+ 20 ^{o}c , 280^{o}c + 20^{o} c and at 450^{o}c + 20^{o} c for 6 months

J. Padmavathy,et.al.,[47] prepared a Ofloxacin floating tablets to enhance the bioavailability and therapeutic efficacy of the drug. Different formulations were formulated by wet granulation technique using HPMC K4M , HPMC K15M and HPMCK100M (floating agent) as polymers along with sodium bicarbonate as gas generating agent. The formulations were evaluated for their physicochemical properties, buoyancy lagtime, total floating time, swelling index and invitro drug release. It was found that hardness of the tablets affects the Buoyancy characteristic of the dosage form. All six formulations possessed good floating properties with total floating time between 8 – 12 hrs. The *invitro* cumulative % drug release of the formulations F1A, F1B, F2A, F2B,F3A and F3B were 102.85% , 101.32% , 100.2% , 99.98%, 99.28% and 97.25% respectively.

Manoj, et al., [48] prepared a floating drug delivery system of diltiazem hydrochloride using polymers such as hydroxypropylmethylcellulose K100M CR and compritol 888 ATO, alone and in combination. The effect of sodium

bicarbonate and succinic acid on drug release was investigated. The high level of both methocel K100M CR and compritol 888 ATO favours the preparation of floating controlled release of diltiazem tablets. It was observed that incorporation of succinic acid in the formulation nullified the effect of the acidic dissolution media on the drug release in this formulation, methocel K100M CR retarded the release by diffusion mechanism and compritol 888 ATO decreased the hydration of matrix and retarded the release by erosion mechanism owing to its hydrophobic property. Together, these polymers retard the release of drug using different mechanisms.

Inez Jimenez et al.,[49] developed a sustained delivery of captopril from floating matrix tablets. The study was done using metolose SH4000/ sodium bicarbonate and at two different compaction pressures. The observation showed that the matrices compacted at lower pressure (55MPa) floated in the dissolution medium for more than 8hr while those compacted at (165MPa) floated only when sodium bicarbonate is included in the formulation. The matrix density is lower when compacted at lower pressure keep more entrapped air, decreasing the agglomerate density and allowing the tablets float, on the other hand, tablets compacted at higher pressure were less porous and displayed a density not allowing the matrices floatation. An increasing proportion of the swelling polymer in the matrix increases. The increasing proportion of the swelling polymer in the matrix increased the maximal hydration volume as well as the time necessary to attain it. The release profiles of captopril form metolose matrices display greater percentages of drug released compared to similar matrices containing sodium bicarbonate due to an obstruction effect of the diffusion path by carbon dioxide bubbles.

Patel et al.,[50] Investigated an intragastric drug delivery system for cefuroxime axetil to evaluate the contribution of HPMC K4M/HPMC K100 LV ratio and the SLS on drug release. Formulations were evaluated for *in vitro* buoyancy and drug release study using USP II paddle type dissolution apparatus using 0.1 N HCl as a dissolution medium. It was found that the polymer blend and SLS greatly affected the dissolution Parameters

Nur and Zhanj et al.,[51] prepared Captopril floating and bioadhesive tablets using two grade of HPMC (400 and 15000cps) and carbopol 934P. *In vitro* dissolution was

carried out in simulated gastric fluid (enzyme free) at 37 ± 0.1°C using the USP type II method. Compared to conventional tablets, release of captopril from these floating tablets was apparently prolonged (24hrs). Tablet hardness was found to be a determining factor with regard to the buoyancy of the tablets.

Chen and Hao et.al.,[52] studied the *in vitro* performance of floating sustained release capsule of verapamil. Capsules filled with mixture of verapamil, HPC and effervescent materials are proposed to provide floating and sustained release for over 10 hrs. The effects of weight filled in the capsule, amount of HPC and the addition of effervescent material on the dissolution kinetics were studied. They concluded that the release of Verapamil from the capsule followed Higuchi release model. However, when effervescent material was added, the system showed a zero-order release.

Desai and Bolton,et.al.,[53] developed controlled release floating tablets of the theophylline using agar and light mineral oil. Tablets were made by dispersing drug and mineral oil mixture in a warm agar solution. The resultant mixture was poured into tablets moulds, which on cooling and air-drying formed floated CR tablets. The light mineral oil was essential for the floating property of the tablets since relatively high amount of the drug (75%) was used.

Hilton and Deasy,et.al.,[54] fabricated an oral sustain release floating tablets of amoxicillin trihydrate using various hydrophilic polymers like Hydroxy Propyl cellulose, Sodium alginate, Sodium carboxymethylcellulose, HPMC and methylcellulose . The report revealed that the intrinsic dissolution studies at p^H 2 showed a decreased drug residence time. They carried out the *in vitro-in vivo* evaluation of dosage form. They finally concluded that their relative bioavailability was reduced and their pharmacokinetic parameters indicated lack of improved efficacy.

K.Gnanaprakash et.al.,[55] developed a floating controlled release drug delivery system of famotidine to increase the gastric retention time of the dosage form and to control drug release. The present work investigates in*vivo* buoyancy and pharmacological activity of prepared floating tablets of famotidine as model drug

delivery system. The best formulation was selected based on *in vitro* characteristics and was used *In vivo* radiographic studies by incorporating $BaSO_4$. The floating formulation showed excellent buoyancy and better gastric cytoprotection when compared with conventional dosage form

Patil UK, et.al., developed amlodipine besylate effervescent floating tablets in ten different formulations (F1 to F10) by employing different grades of polymers and effervescent agents such as sodium bicarbonate and citric acid. The formulations were evaluated for various physical parameters, buoyancy studies, dissolution parameters and drug released mechanisms. F10 formulation showed maximum floating time of 24 hours and gave slow and maximum drug release of Amlodipine besylate spread over 24 hours and whereas Amlodipine besylate released from marketed tablet was rapid and maximum within 12 hours.

R. S. Thakur, et.al., designed floating matrix tablets to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. With this objective, floating dosage form containing clarithromycin as drug was designed for the treatment of *Helicobacter pylori*. Tablets containing hydroxypropylmethylcellulose(HPMC), drug and different additives were compressed using wet granulation and D-optimal design technique.The study showed that tablet composition and mechanical strength have great influence on the floating properties and drug release. Incorporation of gas-generating agent together with polymer improved drug release, besides optimal floating (floating lag time <30 s; total floating time >10 h). The drug release was sufficiently sustained(more than 8 h) and anomalous diffusion as well as zero-order was confirmed. Optimization of the evaluating parameters with ëdesign expertí software was employed to get final optimized formulation. The optimized formulation was obtained using 62.5% clarithromycin, 4.95% HPMC K15M, 18.09% HPMC K4M, 12.96% sodium bicarbonate which gave floating lag time < 30 secs with a total floating time > 10 h, *in vitro* release profile very near to the target *in vitro* release profile and follows anomalous diffusion as well as zero order pattern of release.

Rajesh Kaza et.al., prepared ranitidine hydrochloride sustained release formulation for 24 hrs. Various formulations were prepared by wet granulation technique using the polymers, such as HPMC K100M and HPMC K15M. It was found that the best formulation RT8 was having the floating lag time of 120 sec and showed 98.4% drug release at the end of 24 hours. This way the best formulation was achieved by using the combination of high and low viscous polymers HPMC K100M and HPMC K15M in the ratio of 1:1. *In-vitro* drug release studies of Ranitidine hydrochloride sustained release floating tablets showed that, the rate of drug release is diffusion controlled and follows zero order kinetics the release profile and achieved gastric retention for the desired period of time.

V.F. Naggar et.al.,[56] reported a sustained release system for ketoprofen to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microparticles by the emulsion-solvent diffusion technique. Four different ratios of Eudragit S100 (ES) with Eudragit RL (ERL) were used to form the floating microparticles. The drug retained in the floating microparticles decreased with increase in ERL content. X-ray and DSC examination showed the amorphous nature of the drug. Release rates were generally low in 0.1 N HCl especially in presence of high content of ES while in phosphate buffer pH 6.8, high amounts of ES tended to give a higher release rate. Floating ability in 0.1 N HCl, 0.1 N HCl containing 0.02% Tween 20 and simulated gastric fluid without pepsin was also tested. The formulation containing ES:ERL1:1 (FIII) exhibited high percentage of floating particles in all examined media.

Baumgartner S, et al.,[57] developed floating matrix tablets containing hydroxyl propyl methyl cellulose, which after oral administration are designed to prolong the gastric residence time, increased the bioavailability and diminished the side effects of irritating drugs. The importance of the composition optimization, the formulation effects and characterization of the tablets were examined. The investigation showed that the tablet composition and mechanical strength have great influence on the floating and drug release properties of the tablets. They concluded that the drug release from the tablets followed non-fickian transport.

Jimenez-casttellanos, et.al.,[58] designed and tested the invitro floating and bioadhesive property of sotalol for oral application. Tablets were prepared by mixing the active ingredient with sodium carboxy methyl cellulose, hydroxy propyl cellulose and sodium bicarbonate to generate gas. *In vitro* tests for release of drug, floating and bioadhesion of the tablets were carried out. They concluded that this system showed good characteristics for controlled drug delivery system

Park, et al.,[59] developed and evaluated floating beads from sodium alginate solution containing $CaCO_3$ or $NaHCO_3$ as gas-forming agents with riboflavin as a model drug. *In vitro* release studies revealed that $CaCO_3$ is superior to $NaHCO_3$ as gas forming agent in alginate bead preparations, with enhanced buoyancy and sustained release properties making them excellent for floating drug delivery system.

Chapter III

Aim and Objective of Work

3. AIM AND OBJECTIVE

- The aim of the present work is to formulate and evaluate floating controlled release tablet formulations of carvedilol by using natural polymers like xanthan gum and guar gum.

- Carvedilol is a non-selective $\alpha_{1,}$ $\beta_{1,}$ β_{2} -adrenergic antagonist used in the treatment of hypertension and stable angina pectoris..Carvedilol is selected as a model drug for this investigation because its oral dose is 3.125mg to 25mg twice a day, having low molecularweight (406.48), short biological half-life(2-6hrs) and poor bioavailability(25-30%) due to extensive hepatic first pass metabolism.

- As carvedilol has higher absorption in the proximal region of the GI tract and poor absorption in colon, suggest it is an ideal candidate for a gastroretentive drug-delivery system that will prolong the gastric residence time of the dosage form.

- Naturally occurring polymers is preferred for controlled release formulation because of its low cost, naturally available, biocompatible and better patient tolerance as well as public acceptance.

- So, planned to formulate and evaluate floating controlled release tablets of carvedilol by using natural polymers.

Chapter IV

Plan of Work

4. PLAN OF WORK

The proposed work was carried out to formulate and evaluate floating controlled release tablets of carvedilol in the following phases:

Phase-I:

- Pre-formulation study of carvedilol
- Drug excipient compatibility study of carvedilol

  by Fourier transform infrared spectroscopy (FT-IR)
- Preparation of standard curve of carvedilol In 0.1 N HCL

Phase-II:

- Formulation of floating matrix tablets of carvedilol.
- Evaluation floating matrix tablets of carvedilol
  - Physical evaluation
  - *Invitro* Dissolution study
  - Kinetic study

Phase-III:

Accelerated stability study of the optimized formulation as per ICH Guidelines.

Chapter V

Theoritical Background

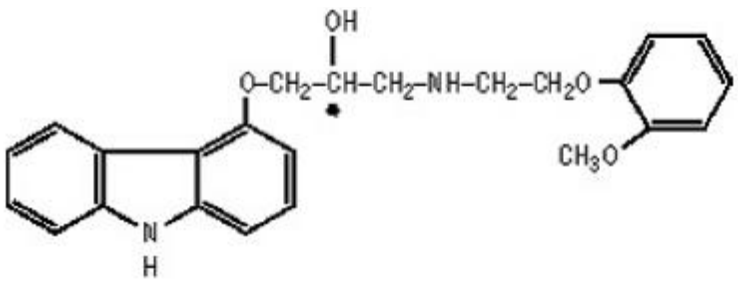
5. THEORETICAL BACKGROUND PROFILES

DRUG PROFILE:

CARVEDILOL[60,61,62,63]:

Carvedilol is a nonselective β-adrenergic blocking agent with α_1-blocking activity.

CHEMICAL STRUCTURE:



CHEMICAL NAME:

(±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol.

Molecular Formula: $C_{24} H_{26} N_2 O_4$

Molecular Weight: 406.5

Category: α and β-Adrenergic antagonist.

Description: A white to off-white powder.

Solubility:

Freely soluble in dimethyl sulfoxide, soluble in methanol and methylene chloride, sparingly soluble in 95%ethanol and isopropanol, slightly soluble in ethyl ether and practically insoluble in water, simulated gastric fluid and intestinal fluid.

Storage:

Store below 30^{o}c, protect from moisture. Store in tight light resistant container.

Mechanism of action:

Carvedilol blocks the binding of Norepinephrine to $\alpha_{1,}$ $\beta_{1,}$ β_{2} receptors which slowers the heart rhythm and reduces the force of heart's pumping which lowers pressure and reduces heart failure.

Clinical Pharmacology:

Norepinephrine stimulates the nerves that control the muscles of the heart by binding to the β_1-, β_2- and α_1-adrenergic receptors causing them to constrict and raise blood pressure. Carvedilol blocks the binding to those receptors, which both slows the heart rhythm and reduces the force of the heart's pumping. This lowers blood pressure and reduces heart failure. Relative to other beta blockers, carvedilol has minimal inverse agonist activity. This suggests that carvedilol has a reduced negative chronotropic and inotropic effect compared to other beta blockers, which may decrease its potential to worsen symptoms of heart failure.

Pharmacodynamics:

Carvedilol produces its antihypertensive effect partly by reducing total peripheral resistance by blocking α_1-adrenoreceptors and by preventing β-adrenoreceptor mediated compensatory mechanisms. This combined action avoids many of the unwanted effects associated with traditional β-blocker or vasodilator therapy.

Renal effects:

Plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment. Based on mean AUC data, approximately 40% to 50% higher plasma concentrations of carvedilol were observed in hypertensive

patients with moderate to severe renal impairment compared to a control group of hypertensive patients with normal renal function.

Pharmacokinetics:

Absorption

Carvedilol is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability

Distribution

The drug is highly lipophilic and is highly protein bound. The stereoselective tissue distribution of carvedilol enantiomers results from an enantiomeric difference in plasma protein binding rather than in tissue binding.

Metabolism

Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with β-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for β-blockade. Compared to carvedilol, the 3 active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about one-tenth of those observed for carvedilol and have pharmacokinetics similar to the parent.

Elimination

The metabolites of carvedilol are excreted primarily via the bile into the feces. The elimination half-life of carvedilol generally ranges from 7 to 10 hours.

Contraindications

- Bronchial asthma or related bronchospastic conditions.
- Second- or third-degree AV block
- Sick sinus syndrome
- Severe bradycardia (unless a permanent pacemaker is in place)
- Patients with cardiogenic shock or who have decompensated heart failure requiring the use of intravenous inotropic therapy.
- Patients with severe hepatic impairment
- Patients with a history of a serious hypersensitivity reaction (e.g., Stevens-Johnson syndrome, anaphylactic reaction, angioedema).

Therapeutic indications: carvedilol can be used in the following indications:

- Hypertension
- Congestive heart failure
- Myocardial infarction

Marketed dosageforms:

Carvil, COREG®, Coreg CR controlled release tablets of Carvedilol in doses 3.125mg, 6.25mg, 12.5 mg and 25mg.

5.2 POLYMER PROFILE:

5.2.1 Xanthum Gum[64]:

Nonproprietary Names

BP : Xanthan gum.

USPNF : Xanthan gum.

Synonyms : Keltrol;Corn sugar gum;Rhodigel;Xantural;Polysaccharide B-1459

Empirical Formula and Molecular Weight:

Formula : $(C_{35}H_{49}O_{29})n$

M.Wt **:** Approximately 2×10^6

Functional Category

Stabilising agent,Suspending agent,Viscosity increasing agent.

Applications in Pharmaceutical Formulation or Technology

Xanthum gum is widely used in oral and topical formulations,cosmetics and foods as a suspending agent and stabilising agent.It is also used as a thickening agent and emulsifying agent.It is nontoxic,compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over a wide PH and temperature range. Xanthan gum gels show pseudo plastic behaviour, the shear thining being directly proportional to the shear rate.The viscosity returns to normal immediately on release of shear stress.

Recent studies have revealed that xanthan gum can also used as an excipient for spray drying and freeze dryng processes for better results.

Although primarily used as a suspending agent,xanthan gum has also been used to prepare sustained release matrix tablets. Xanthan gum has been incorparated

in an ophthalmic liquid dosage form, which interacts with mucin there by helping in the prolonged retention of the dosage form in the precorneal area.

Xanthan gum can be used to increase the bioadhesive strength in vaginal formulations and as a binder in colon specific drug delivery systems. Xanthan gum is also used as a hydrocolloid in the food industry and in cosmetics it has been used as a thickening agent in shampoos.

Description

Xanthan gum occurs as a cream or white colored, odourless,free-flowing,fine powder

Typical Properties

Acidity/alkalinity **:** p^H=6.0-8.0 for a 1%w/v aqueous solution

Freezing point **:** 0^oC for a1% w/v aqueous solution

Heat of combustion **:** 4.6 j/g(3.5 cal/g)

Melting point **:** chars at 270^oC

Solubility:

It is practically insoluble in ethanol and ether; soluble in cold or warm water.

Viscosity:

1200-1600 mPas(1200-1600 Cp) for a 1% w/v aqueous solution at 25^oC

Specific gravity:

1.600 at 25^0C

Xanthan gum is a stable material.aqueous solutions are stable over a wide P^H range (P^H 3-12),although they demonstate maximum stability at (P^H 4-10) and temperatures of 10-60^{0}C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example,viscosity is reduced.solutions are also stable in the presence of enzymes,salts,acids,and bases.

Storage conditions :

The bulk material should be stored in a well-closed container in a cool,dry place.

Incompatibilities:

Xanthan gum is incompatible with oxidising agents,some tablet film-coatings,carboxy methylcellulose sodium, dried aluminium hydroxide gel and some active ingredients such as amitriptyline,tamoxifen and verampil.

Safety:

Xanthum gum is widely used in oral and topical pharmaceutical formulations,cosmetics and food products and is generally regarded as nontoxic and nonirritant at the levels empolyed as a pharmaceurtical excipient. The estimated acceptable daily intake for xanthan gum has been set by the WHO at up to 10 mg/kg body weight.

Related substances:

Guar gum; ceratonia

5.2.2 GUAR GUM[65]:

Nonproprietary Names

BP : Guar galactomannan;

PhEur : Guar galactomannanum;

USPNF : Guar gum.

Synonyms : Galactosol; Guar flour; Jaguar gum; Meyprogat; Meyprodor; Meyprofin.

Empirical Formula and Molecular Weight

Formula: $(C_6H_{12}O_6)n$ **M.Wt**: 2,20,000

Structural Formula

Guar gum consists of linear chains of (1→4)-β-d-mannopyranosyl units with α-d-galactopyranosyl units attached by (1→6) linkages. The ratio of d-galactose to d-mannose is between 1: 1.4 and 1: 2.

Functional Category

Suspending agent, tablet binder, tablet disintegrant and viscosity increasing agent.

Applications in Pharmaceutical Formulation or Technology

Guar gum used in the preparation of sustained release matrix tablets in the place of cellulose derivatives such as methylcellulose. It is used in solid dosage forms as a binder and disintegrant, in oral and topical products as a suspending, thickening, and stabilizing agent; and also as a controlled release carrier. Guar gum has also been examined for use in colonic drug delivery.

Table No.3: Uses of Guar gum:

Use	Concentration (%)
Emulsion stabilizer	1
Thickener for lotions and creams	Up to 2.5
Tablet binder	Up to 10

Description

Guar gum obtained from the ground endosperms of *Cyamopsis tetragonolobus* (L.) Taub. (Leguminosae). It consists chiefly of a high-molecular-weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycoside linkages, which may be described chemically as a galactomannan. Guar gum occurs as an odorless or nearly odorless, white to yellowish-white powder with a blend taste.

Typical Properties

p^H = 5.0–7.0 (1% w/v aqueous dispersion)

Solubility:

It is practically insoluble in organic solvents. It swells almost immediately to form a highly viscous and thixotropic solution in cold or hot water,

Viscosity:

4.86 Pa s (4860 cP) for 1% w/v dispersion.

Stability and Storage Conditions:

Guar gum powder should be stored in a well closed container in a cool and dry place.

5.3 EXCIPIENT PROFILE:

5.3.1 SODIUM BICARBONATE[66]:

Nomenclature

Non-proprietary names:

JP : Sodium bicarbonate

BP : Sodium bicarbonate

PhEur : Natriihydrogencarbonas

USP : Sodium bicarbonate

Chemical Name: Carbonic acid monosodium salt

Formula:

Structural Formula : $NaHCO_3$

Physical and chemical properties:

Molecular weight **:** 84.01

Color **:** White

Nature **:** Crystalline powder

Odour **:** Odourless

Taste **:** Saline/slight alkaline

Density **:** 0.869-2.173 g/cm^3

Moisture content **:** less than 1%w/w

Solubility **:** Soluble in water, practically insoluble in ethanol(95%) and ether.

Osmolarity **:** 1.39% w/v aqueous solution is iso osmotic with serum.

Melting point **:** 270 °C (with decomposition)

Functional category:

Alkalizing agent, therapeutic agent

Applications:

- Used in pharmaceutical formulation as a source of carbon dioxide in effervescent tablets and granules.
- Used to produce or maintain an alkaline pH in a preparation, like solution of Erythromycin, Lidocaine, and Niacin etc.
- Used to produce a sodium salt of the active ingredient that has enhanced solubility.
- Used as a freeze-drying stabilizer and in toothpaste.
- Used as a gas forming agent in alginate raft system and in floating drug delivery system.

Stability and Storage:

Sodium bicarbonate is stable in dry air but slowly decomposed in moist air and should therefore be stored in well-closed container in a cool dry place.

Safety:

Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence.

5.3.2 LACTOSE[67]:

Nonproprietary names:

Lactose (BP), Lactose Monohydrate (PhEUR, USP-NF).

Synonym:

CapsuLac, GranuLac, Lactochem, lactosummonohydricum, monohydrate, Pharmatose, PrismaLac, SacheLac, SorboLac, pheroLac, SuperTab 30GR, Tablettose.

Chemical Name and CAS Registry Number:

O-b-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate,[10039-26-6]

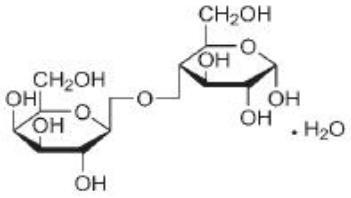
Emprical Formula and molecular weight:

Formula : $C_{12}H_{22}O_{11}\cdot H2O$. MW: 360.31

Description:

In solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α lactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder, it is odorless and slightly sweet-tasting.

Structural formula:



P^H **:** 5.5-8.9.(1%w/w aqueous solution at 25^o)

Solubility **:** Insoluble in chloroform, ethanol, ether. Soluble in water in ratio of 1 in 5.24

Melting point **:** 201–202^0C (for dehydrated a-lactose monohydrate)

Moisture content:

Lactose monohydrate contains normally had a range of 4.5–5.5% w/w water content.

Functional Category:

Dry powder inhaler carrier, lyophilization aid, tablet binder, tablet and capsule diluent, tablet and capsule filler.

Applications in Pharmaceutical formulation or technology:

Lactose is widely used as a filler and diluent in tablets and capsules. Lactose is also used as a diluent in dry-powder inhalation. Lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose to prepare sugar-coating solutions. It may also be used in intravenous injections. Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Direct-compression grades of lactose monohydrate are available as spray-dried lactose and anhydrous lactose.

Incompatibilities:

A Millard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, amphetamines and lisinopril.

Stability and storage conditions:

Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. Solutions show mutarotation. Lactose should be stored in a well-closed container in a cool, dry place.

Safety:

Lactose is widely used as a filler and filler-binder in orals and injections. Adverse reactions to lactose are largely attributed to lactose intolerance, results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence.

5.3.3 MAGNESIUM STEARATE[68] :

Non proprietary name :

BP : magnesium stearate,

JP : magnesium stearate,

Pheur : magnesiistearas,

USPNF : magnesium stearate.

Synonyms :

Magnesiumoctsdecanoate; octadecanoicacid, magnesium salt; stearic acid, magnesium salt

Chemical name and CAS Registry number :

Octadecanoic acid magnesium salt [557-04-0]

Emperical formula :

$C_{36}H_{70}MgO_4$

Molecular weight :

591.34

Functional category :

Tablet and capsule lubricant

Application in pharmaceutical formulation or technology:

Magnesium stearate is widely used in cosmetics, foods and in pharmaceutical formulation. It is primarily used as a lubricant in capsule and tablet manufacture.

Description :

Magnesium stearate is a very fine, light white, precipitated or mild, implantable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greesy to touch and readily adheres to the skin.

Chapter VI

Materials and Methods

6.MATERIALS AND METHODS

The list of materials and equipments used were illustrated in the table no's 4 &5.

6.1.1 LIST OF MATERIALS

Table no.4: materials and their suppliers

S.No.	MATERIAL	SUPPLIED BY
1	Carvedilol	cadila pharma, Ahmedabad
2	Xanthum gum	cadila pharma, Ahmedabad
3	Guar gum	cadila pharma , Ahmedabad
4	*Sodium bicarbonate*	cadila pharma, Ahmedabad
5	Lactose	S.D. Fine chemical Pvt Ltd, Mumbai
6	Magnesium sterate	S.D. Fine chemical Pvt Ltd, Mumbai
7	Hydrochloric Acid	Merck specialties Pvt Ltd, Mumbai
8	Methanol	S.D. fine chemical Pvt Ltd, Mumbai

6.1.2 LIST OF INSTRUMENTS

Table No.5: Equipment and their manufacturer

S.No.	INSTRUMENTS	MANUFACTURER
1	Electronic balance	Shimadzu ELB-300
2	Sieve no 40	Jaico metals
3	Tablet compression machine	Instruments&chemicals pvt Ltd,India
4	*Tablet hardness tester*	Monsanto
5	Friability test apparatus	Roche Friabilator
6	Tablet dissolution apparatus	Lab India
7	Stability control oven	Biotechno lab, BTL
8	UV-Visible spectrophotometer	Lab India,Lambda 25
9	FTIR spectrophotometer	Bruker Alpha-T

6.2 PREFORMULATION STUDIES:

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances in order to develop stable, safe and effective dosage forms.

The following preformulation studies were Performed:

- Study of organoleptic properties
- Solubility analysis
- Melting point of drug
- Drug powder characterization
- drug-excipients compatibility study by FT-IR

6.2.1 Organoleptic properties:

Colour: a small quantity of pure carvedilol powder was taken in a butter paper and viewed in well illuminated place.

Taste and odour: very less quantity of carvedilol was used to get taste with the help of tongue as well as smelled to get the odour.

6.2.2 Solubility analysis[69]:

Solubility is important pre-formulation parameter because it affects the dissolution and bio availability of drug.

Method: Solubility of carvedilol was determined in methanol, ethanol, dimethyl fluoride, methylchloride,0.1NHCl.Solubility studies were performed by taking excess amount of carvedilol in different beakers containing the solvent. The mixture

was shaken for 10hrs at regular intervals. The solution was filtered by using whatmann filter paper. The filtered solution were analysed spectrophotometrically.

6.2.3 Melting point[70]:

The melting point of carvedilol was determined by capillary method, using small quantity of carvedilol was taken and placed in apparatus and determined the melting point and matched with standards.

6.2.4 Loss on drying[71]:

Determined on 1 g by drying in an oven at 100°C to 105°C for 3 hours. Mixed and accurately weighed the substance to be tested. Tare a glass stopper, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Weighed the empty bottle (W1). Put the sample in bottle, replaced the cover, and accurately weighed the bottle with contents (W2). By gently, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm. Placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature in desicator before weighing. Weighed the bottle (W3).The difference between successive weights should not less than 0.3%.

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2-W3)}{(W2-W1)} \times 100$$

Where, W1 = Weight of empty weighing bottle

W2 = Weight of weighing bottle + sample

W3 = Weight of weighing bottle + dried sample

6.2.5 Drug powder characterization[72, 73]:

6.2.5.1 Angle of repose: Angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles. The internal angle between the surface of the pile and horizontal surface is known as the angle of repose and is related to the density, surface area and co-efficient of friction of the raw material.

Method: Angle of repose was determined by using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed blend is allowed to pass through the funnel freely on the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\Theta = \tan^{-1} (h/r)$$

Where, h = height of heap, r = radius of heap, Θ = angle of repose.

Table-6: Limits

Angle of repose	**Flow property**
$<25^{o}$	Excellent
$25\text{-}30^{o}$	Good
$30\text{-}40^{o}$	Passable
$>40^{o}$	Very poor

6.2.5.2 Bulk density: Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more spherical in shape, bulk density was increased. In addition as the granule size increases bulk density decreases.

Method: A quantity of 5 gm of powder weighed and transferred to a measuring cylinder . The bulk volume and weight of the powder was determined. Bulk density was calculated using the formula.

Bulk Density = Bulk Mass / Bulk Volume

6.2.5.3 Tapped density: It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder.Then the tapping was done and the tapped volume was noted. The tapped density was calculated by using the following formulae

$$\textbf{Tapped Density} = \frac{m}{Vf}$$

Where, m = initial weight of material in gm, Vf = volume of material after tapping.

Generally replicate determinations are desirable for the determination of this property.

6.2.5.4 Measurement of Powder Compressibility:

Based on the apparent bulk and the tapped density, the percentage compressibility of bulk was determined by the following formula.

$$\textbf{Compressibility index:} = 100\frac{(V_0 - Vf)}{V_0}$$

Where, Vf = final tapped volume, Vo = initial un tapped volume

Table-7: Limits

S.no	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Verypoor
6	>40	Extremelypoor

Hausner's Ratio: $= \frac{V_0}{Vf}$

Where, Vf = final tapped volume, Vo = initial un tapped volume.

Table-8: Limits

S.No	Hausner's ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

6.2.6 COMPATIBILITY STUDY:

6.2.6.1 Drug excipient compatibility studies[76]:

IR spectra of drug, polymer and drug and polymers, individual excipients, drug and polymers and excipients were obtained by using bruker.

Method: Drug and excipients were analyzed by IR spectral studies by using KBr pellet technique. In this method, the drug and KBr were mixed at the ratio of

1:100. Then these mixtures were pressed in to a pellet. The FT-IR spectra were recorded using KBr pellet method in the region 400-4000 cm^{-1}. Spectra were recorded for pure drug, pure excipients, and physical mixture of drug and polymer, drug, polymer and excipients.

6.3 STANDARD CURVE OF CARVEDILOL DRUG:

The calibration curve is based on the spectrophotometry. The maximum absorption was observed at 240nm. It obeyed Beer's law in the concentration range of 2-10 µg/ml.

6.3.1 Preparation of stock and standard solution:

The stock solution was freshly prepared by dissolving 100mg of carvedilol in few ml of methanol in a 100ml volumetric flask and then made up the solution up to the mark using 0.1N HCl for obtaining the solution of strength 1000 µg/mL (stock I). 10ml of this solution is diluted to 100ml with 0.1N HCl to obtain a solution of strength 100 µg/ml (stock II)

6.3.2 Preparation of various concentrations:

10 ml stock solution was taken from stock solution-2 and volume made up to 100 ml by using 0.1 N HCl to get 10 µg/ml concentrations. From this solution with draw 2, 4, 6, 8, 10 ml of solution in to the 10 ml volumetric flask and volume made up to 10 ml by using 0.1N HCl to get the concentrations 2, 4, 6, 8, 10 µg/ml.

6.4 Formulation of carvedilol floating tablets[77]:

Floating controlled release tablets were prepared by direct compression method. Carvedilol was mixed with the required quantities of polymers (xanthan gum, guar gum) sodium bicarbonate (12%), and lactose by geometric mixing. The powder blend was then lubricated with magnesium stearate (2%) and mixed for about 3 minutes. Finally this mixture was compressed on a 16-station rotary tablet machine (Cadmach, Ahmedabad, India) using a 6 mm standard flat-face punches.

Formulation composition of gastroretentive tablets of carvedilol

Table:9 Quantity of Raw materials Per Tablet (In mg)

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Carvedilol	20	20	20	20	20	20	20	20	20
2	Xanthum gum	5	10	-	10	20	-	15	30	-
3	Guar gum	5	-	10	10	-	20	15	-	30
4	Sodium bicarbonate	12	12	12	12	12	12	12	12	12
5	Lactose	56	56	56	46	46	46	36	36	36
6	Magnesium sterate	2	2	2	2	2	2	2	2	2
7	Total weight	100	100	100	100	100	100	100	100	100

6.5 Evaluation of floating tablets of carvedilol:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Following parameters were evaluated

- Tablet thickness
- Weight variation test
- Hardness
- Friability
- Content uniformity

- Buoyancy/floating test
- Swelling studies
- Invitro drug release studies

6.5.1 Tablet thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using vernier calipers. The average thickness and standard deviation were reported.

6.5.2 Weight variation:

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight and standard deviation were calculated and the results were expressed as compliance or non-compliance of set limits.

Table : 10:Weight variation tolerance

Average weight (mg)	% Deviation allowed
130 or less	10
130-323	7.5
More than 324	5

6.5.3 Tablet hardness[78] :

Tablet hardness was measured using a Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. The crushing strength of the 10 tablets with known weight and thickness

of each was recorded in kg/cm^2 and the average hardness and standard deviation was reported.

6.5.4 Friability[79] :

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

6.5.5 Content uniformity[80]:

The formulated carvedilol floating tablets were assayed for drug content.

From each batch of prepared tablets, ten tablets were collected randomly and powdered. a quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 100 ml of methanol was added and then the solution was subjected to sonication for about 2 hours. The solution was made up to the mark with methanol. The solution was filtered and suitable dilutions were prepared with methanol. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 240 nm by using UV-Visible spectrophotometer.

6.5.6 Buoyancy / Floating Test:

The *in vitro* buoyancy was determined by floating lag time. the tablets were placed in a 100-ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

6.5.7 Swelling Index:

The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900ml of distilled water which was maintained at $37^{o} \pm 0.5^{o}$c, rotated at 50 rpm. At selected regular intervals the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU).

$$\%WU = (Wt - Wo) * 100 / Wo$$

Where Wt is the weight of the swollen tablet and Wo is the initial weight of the tablet.

6.5.8 Dissolution study of tablets[81]:

Apparatus	:	Dissolution test apparatus (USP XXIII)
Method	:	USP type 2 apparatus (paddle method)
Dissolution medium	:	0.1N HCl
Volume	:	900 ml
Temperature	:	37 ± 0.5 °C
Speed	:	50 rpm

Procedure

The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr,10hr,12hr,14hr,16hr,20hr, and 24hr. The volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after each sampling.The release studies were conducted with 6 tablets, &determine the mean value.Then the mean values were plotted aganist time.

Each sample was analyzed at 240nm using double beam UV and Visible Spectrophotometer against reagent blank.

The drug concentration was calculated using standard calibration curve.

6.6 KINETIC DATA ANALYSIS[82]:

The analysis of drug release mechanism from a pharmaceutical dosage from is important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first order kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion equation and Peppas-Korsemeyer equation.

6.6.1 Zero Order Release Kinetics:

It defined a linear relationship between the fractions of drug released versus time.

$$\mathbf{Q = k_o t}$$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics

6.6.2 First Order Release Kinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$$\mathbf{In\ (1\text{-}Q) = -\ K_1 t}$$

Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

6.6.3 Higuchi's equation:

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$\mathbf{Q=K_2t^{½}}$$

Where, K2 is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant.

6.6.4 Korsemeyer equation:

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppas and Korsemeyer equation (Power Law).

$$\mathbf{M_t/M_{\sim} = K.t^n}$$

Where, M_t is the amount of drug released at time t and M_α is the amount released at timeα, thus the M_t/M_α is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent. A plot between log of M_t/M_α against log time will be linear if the release obeys Peppas and Korsemeyer equation and the slope of this plot represents "n" value.

Table-11: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion Exponent	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-fickian) diffusion
0.89	Case II transport
n>0.89	Super Case II transport

6.7 Stability Studies:

The optimized formulation was subjected to stability studies as per I.C.H guidelines. Samples were kept at 40^0c with 75% RH and analyzed for weight variation, hardness, friability, drug content and *In vitro* dissolutions study for every month for a period of three months.

Chapter VII

Results and Discussion

7. RESULTS AND DISCUSSION

7.1 PREFORMULATION STUDY

These tests were performed as per procedure given in 6.2.1. The results were illustrated in table no 12.

7.1.1 Organoleptic properties:

Table-12: Observation of organoleptic properties:

TEST	SPECIFICATION	OBSERVATION
Colour	White or almost white powder	White powder
Odour	---	Odourless

7.1.2 Solubility analysis:

Carvedilol samples are examined and it was found to be insoluble in water and slightly soluble in methanol, soluble in dimethyl formamide. It also dissolved in dilute alkali and in dilute acids.

7.1.3 Melting point of drug:

The melting point of carvedilol was determined by capillary method, melting point of carvedilol was found to be 140°C. Melting point compared with USP standards that showed that drug is pure.

7.1.4 Loss on Drying:

It was determined as per procedure given in 6.2.4. The results was given in table no.13

Table-13: **Observations for loss on drying**

Test	Loss on drying	Observation
Loss on drying	Not more than 0.5%	0.41%

The loss drying of drug was founded as0.41 which is with in the limit.

7.1.5 Drug powder characterization:

7.1.5.1 Angle of repose:

It was determined as per procedure given in 6.2.5.1. The results was given in table no.14

Table-14: Angle of repose

Material	Angle of repose
carvedilol Raw material	29.31

The results indicating that the raw material has good flow property.

7.1.5.2 Flow properties:

It was determined as per procedure given in 6.2.5.2 to 6.2.5.4.The results was given in table no.15

Table-15: Flow properties of pure drug

Material	Bulk density	Tapped density	Carr's index (%)	Hausner ratio (%)
caevedilol raw material	0.25	0.43	12	1.128

The results are clearly indicating that the carvedilol raw material has good flow property.

7.1.6 Drug-polymer compatibility study:

FTIR studies:

The FTIR spectra of the pure drug, excipient and physical mixture of drug and excipients used in floating controlled tablet formulations shown in Fig no 9-16 were recorded in between 400-4000 wave number (cm^{-1}).

Fig. No: 9: IR spectrum of carvedilol standard

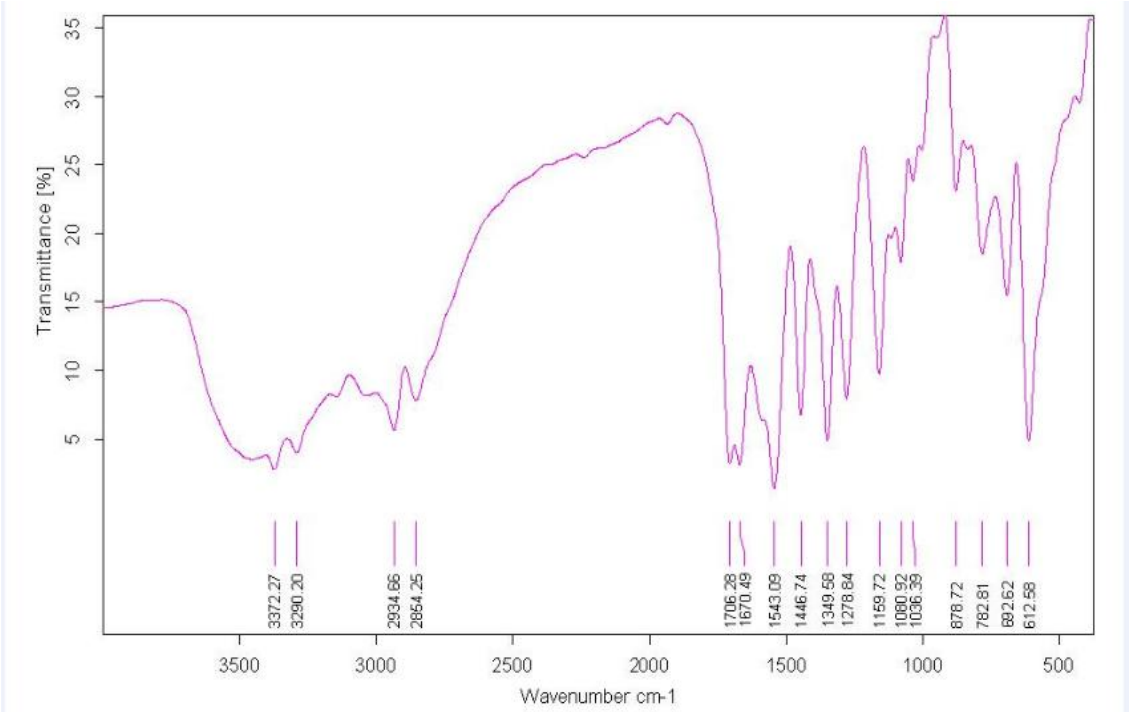


Fig. No: 10: IR spectrum of guar gum

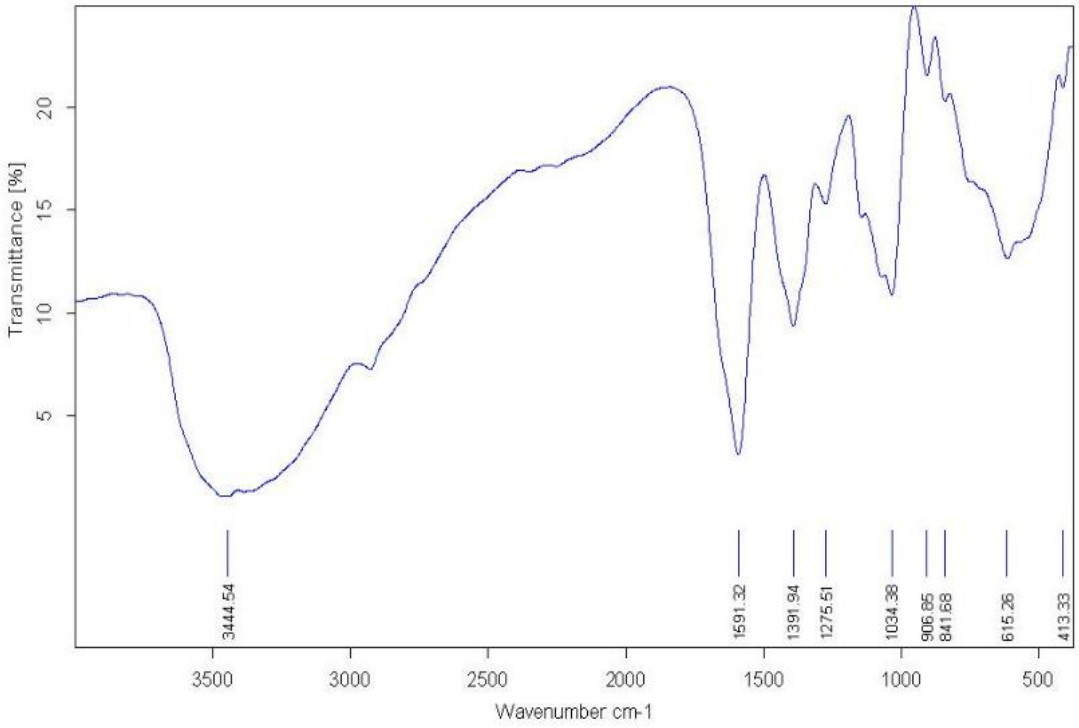


Fig. No: 11: IR spectrum of Xanthan gum

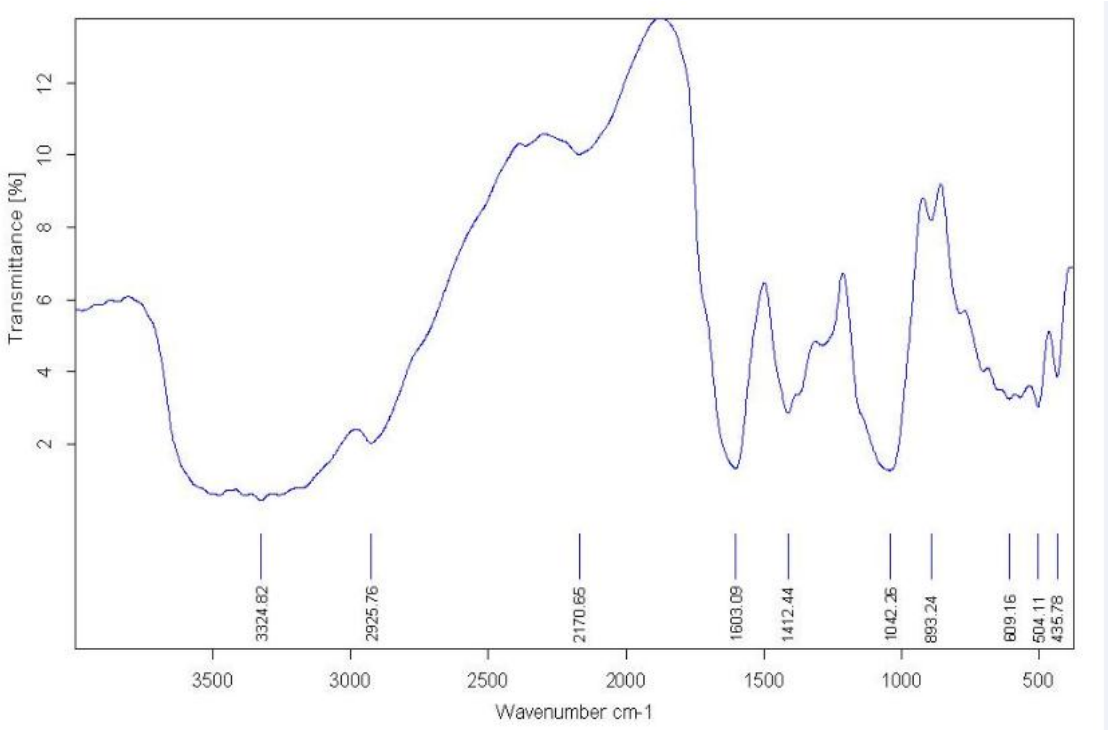


Fig. No: 12: IR Spectrum of carvedilol and polymers

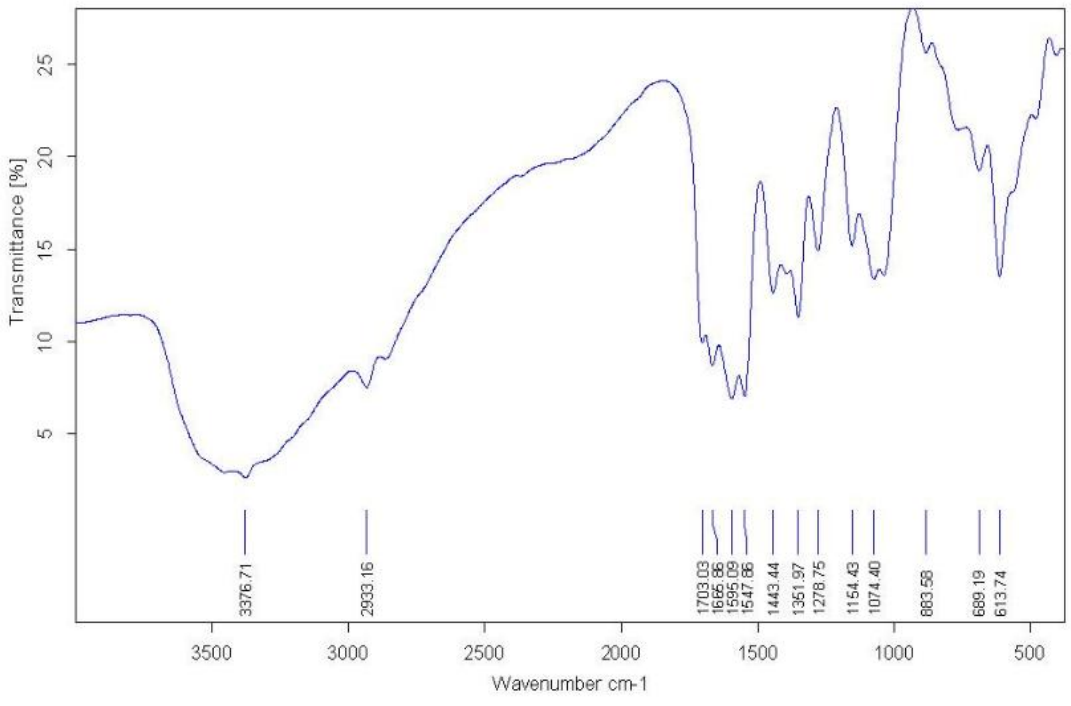


Fig. No: 13: IR Spectrum of Magnesium stearate

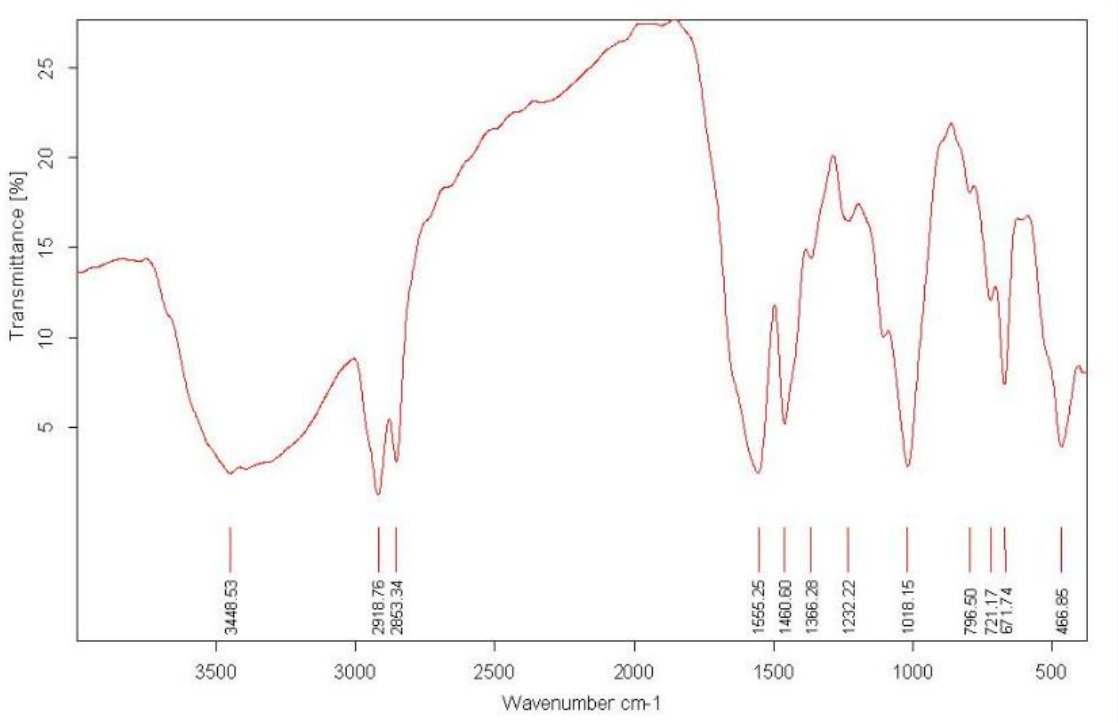


Fig. No: 14: IR Spectrum of Lactose

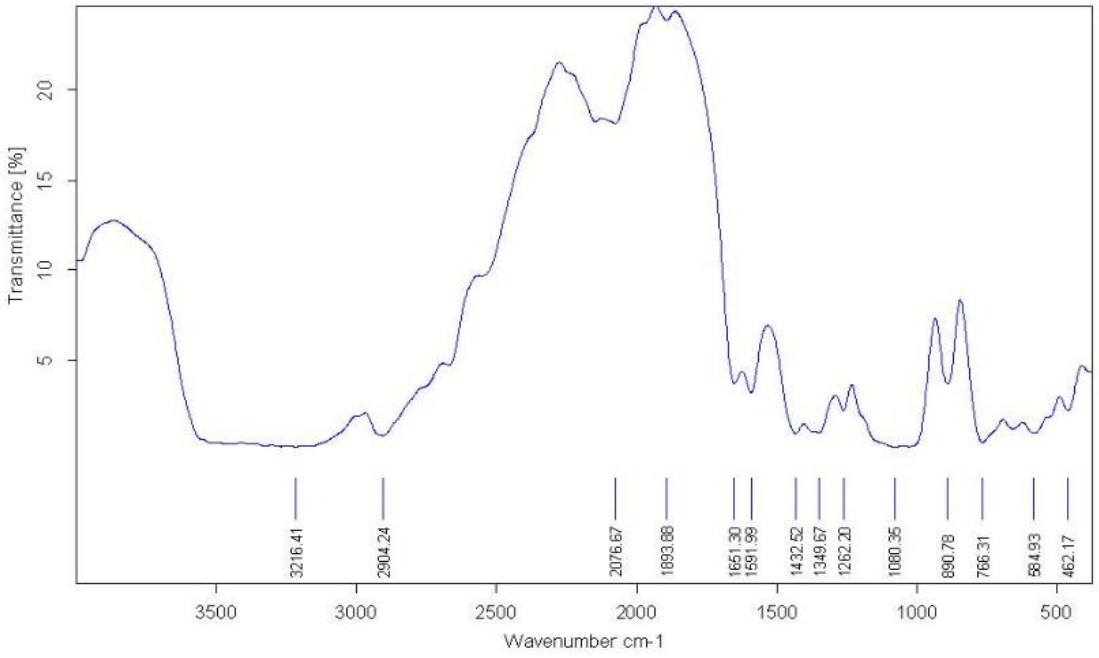


Fig. No: 15 IR Spectrum of Sodium Bicarbonate

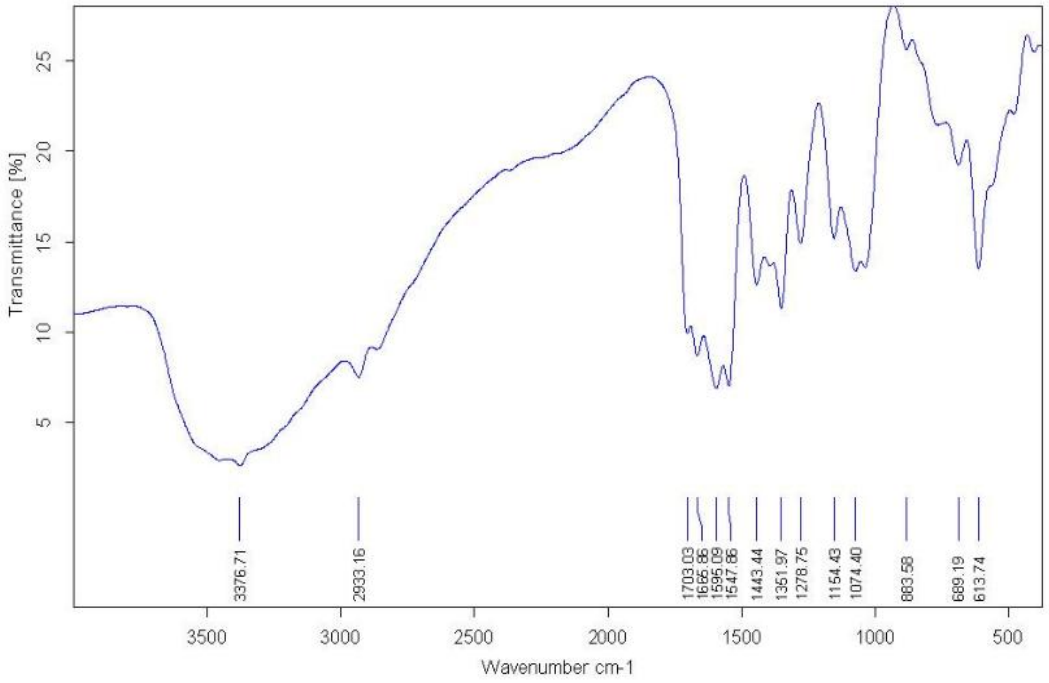


Fig. No: 16: IR Spectrum of carvedilol, polymers and excipients

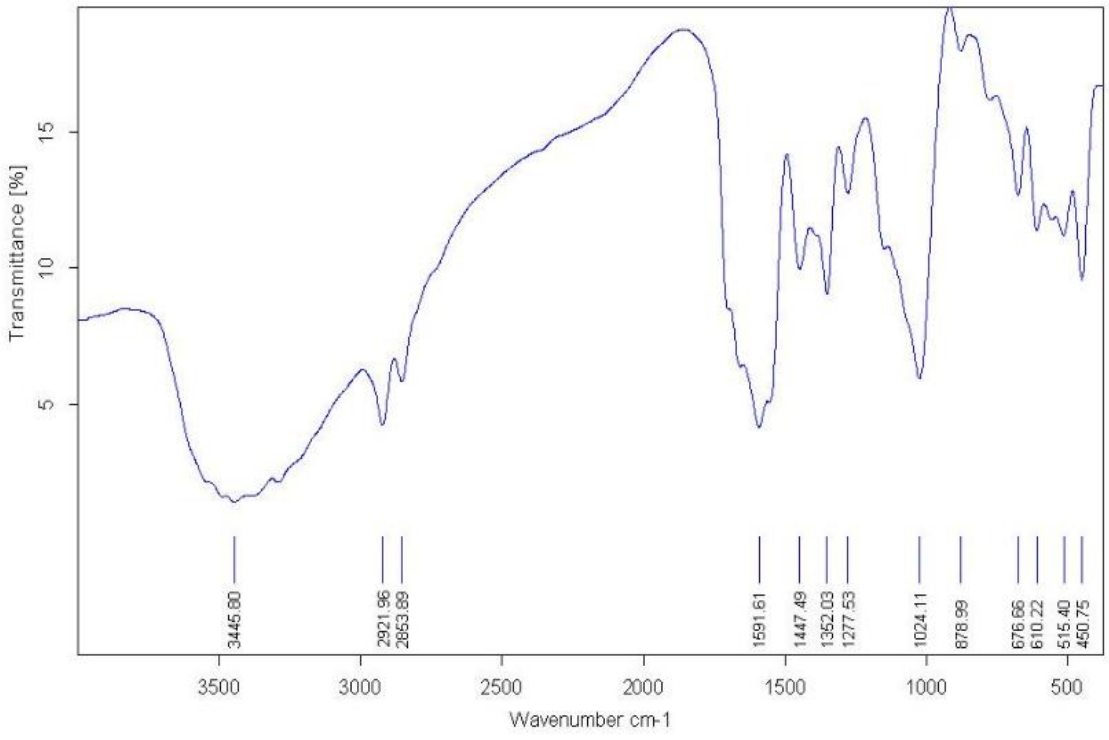


Table 16: FT-IR Peaks of various components

S.No	Peak in pure drug (cm^{-1})	Functional Group	Type of vibration	Peak in Physical mixture
1.	3372.27	Amine (-N-H)	Stretch (medium)	3376.71
2.	2934.66	Aromatic (-C-H)	Stretch (medium)	2933.16
3.	1706.28	Amide (C=0)	Stretch (Strong)	1703.03
4.	1670.49	Methylene cyclohexane	Stretch (Scissoring)	1666.86
5.	1080.92	Sulfoxides	Stretch (Strong)	1074.40
6.	1349.58	Aromatic plane bending (C-H)	Stretch (medium)	1351.97
7.	1543.09	Aromatic (C=C)	Stretch (Weak, multiple)	1547.86

The IR Spectrum of pure drug and physical mixture of drug and polymer were studied.

From the above results functional groups and type of vibrations are noted (Table no : 16) In case of FTIR study no peaks are observed which interfere with the main drug peaks. So,there was no disappearance or appearance of already existing peaks. Hence drugs were found to be comptabile with excipients.

7.2 STANDARD CURVE OF CARVEDILOL PURE DRUG:

Calibration curve of carvedilol was determined by plotting absorbance (nm) versus concentration (µg/ml) at 240 nm. The results were obtained as follows.

Table -17: Standard curve of Carvedilol

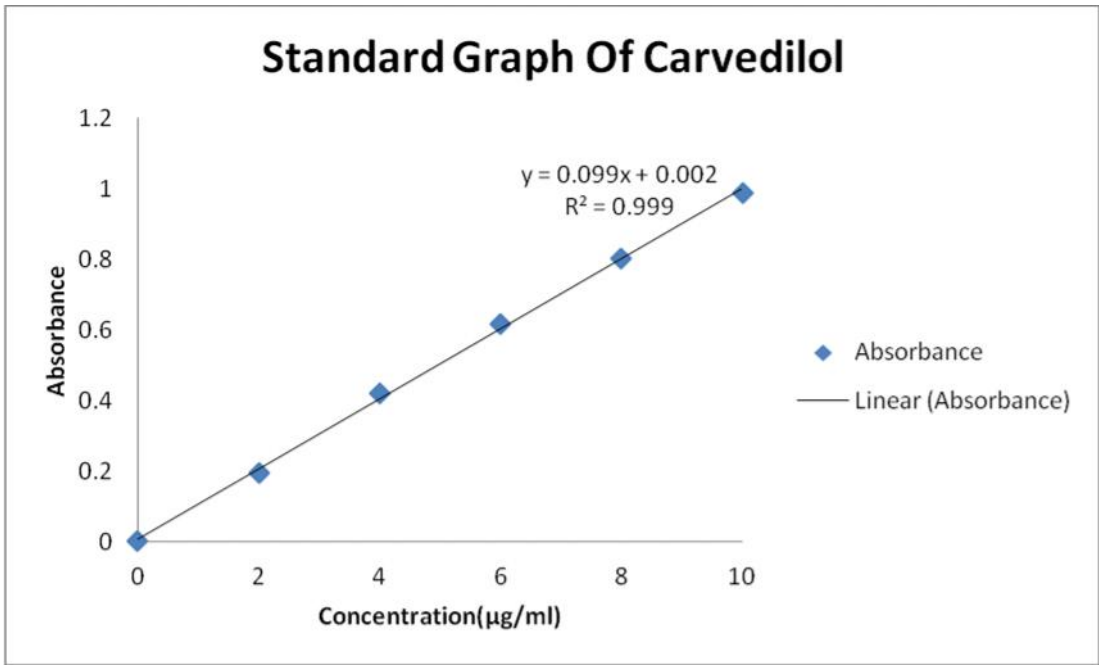
Concentration(µg/ml)	Absorbance(nm)
0	0
2	0.195
4	0.420
6	0.615
8	0.801
10	0.986

The linear regression analysis was done on absorbance data points. A straight line generated to facilitate the calculation of amount of drug, the equation is as follows:

$$Y = mx + c$$

Where Y=absorbance, m=slope, x=concentration

Fig No.17: standard plot for Carvedilol in 0.1 N HCL



7.3 EVALUATION OF PRECOMPRESSION PARAMETERS

The following parameters were carried out by the procedure given in 6.2.5.The results were illustrated in the below table no.18

Table-18: Evaluation of powder characteristics:

Formulation code	Angle of repose (± SD)	BD (gm/ml) ± SD	TD (gm/ml) ± SD	Carr's index(%) (± SD)	Hausner's ratio (± SD)
F1	26.12±0.04	0.317±0.01	0.367±0.02	14.65±0.06	1.08±0.05
F2	27.07±0.01	0.327±0.03	0.389±0.04	15.21±0.07	1.09±0.04
F3	26.04±0.03	0.337±0.06	0.381±0.01	13.63±0.04	1.11±0.02
F4	29.0i±0.07	0.347±0.04	0.391±0.07	16.52±0.01	1.19±0.06
F5	26.97±0.09	0.296±0.03	0.320±0.03	13.12±0.03	1.16±0.03
F6	25.71±0.06	0.260±0.01	0.336±0.01	15.27±0.01	1.15±0.01
F7	26.16±0.03	0.266±0.04	0.372±0.02	14.56±0.04	1.16±0.03
F8	27.11±0.09	0.307±0.05	0.332±0.03	13.41±0.07	1.17±0.05
F9	26.16±0.04	0.312±0.02	0.356±0.01	16.31±0.05	1.18±0.04

Angle of repose for all formulations were examined .The values were found to be within the range from 26.04±0.03 to 29.01±0.07. This indicated that powder blend having good flow property.

The bulk density and tapped density values were found to be within the range from 0.260±0.01 to 0.347±0.04 and 0.320±0.03 to 0.391±0.07 respectively.

The Hauser's ratio values were found to be within the range from 1.08±0.05 to 1.19±0.06.This indicated that powder blend having good flow property.

7.4 EVALUATION OF FORMULATED TABLETS

Table-19: Evaluation of formulated tablets

Formulation code	Weight variation in mg (± SD)	Hardness in kg/cm^2 (± SD)	Friability (%)	Drug content (± SD)	Thickness in mm (± SD)
F1	101±2.99	4.5±0.34	0.47	98.76±0.19	1.3±0.12
F2	100±1.98	4.2±0.73	0.68	99.16±0.27	1.2±0.21
F3	99±3.7	4.4±1.92	0.47	100.87±0.41	1.3±0.53
F4	100±6.5	4.3±0.34	0.46	100.92±0.21	1.3±0.16
F5	100±1.3	4.6±0.28	0.72	98.48±0.26	1.3±0.42
F6	99±6.59	4.3±0.37	0.74	99.67±0.17	1.2±0.53
F7	101±1.6	4.4±0.89	0.63	99.87±0.32	1.3±0.24
F8	99±3.06	4.3±0.42	0.45	99.28±0.33	1.2±0.16
F9	100±3.9	4.4±0.56	0.83	98.87±0.16	1.2±0.29

The formulated floating tablets were then evaluated for various physical characteristics like thickness, weight variation, hardness, friability, drug content. The weight variation of tablets was uniform in all formulations and ranged from 99±0.02 to 101±0.06.The % deviation was coming within 8% to 10 % range. for 100 mg tablet the accepted % deviation should be 10 % .F1-F9 batches came within limit and passed the test. The hardness of the prepared tablets was ranged from 4.2±0.73 to 4.5±0.2, friability values were ranged from 0.45 to 0.83 which fallen within the limit of standard (0.1 to 0.9%). Drug content of tablets was ranged from 98.76±0.19 to 100.92±0.21, F4 showed maximum drug content. Thickness of tablets was uniform and values are ranged from 1.2±0.000 to 1.3±0.011.

7.4.1 Buoyancy / Floating Test:

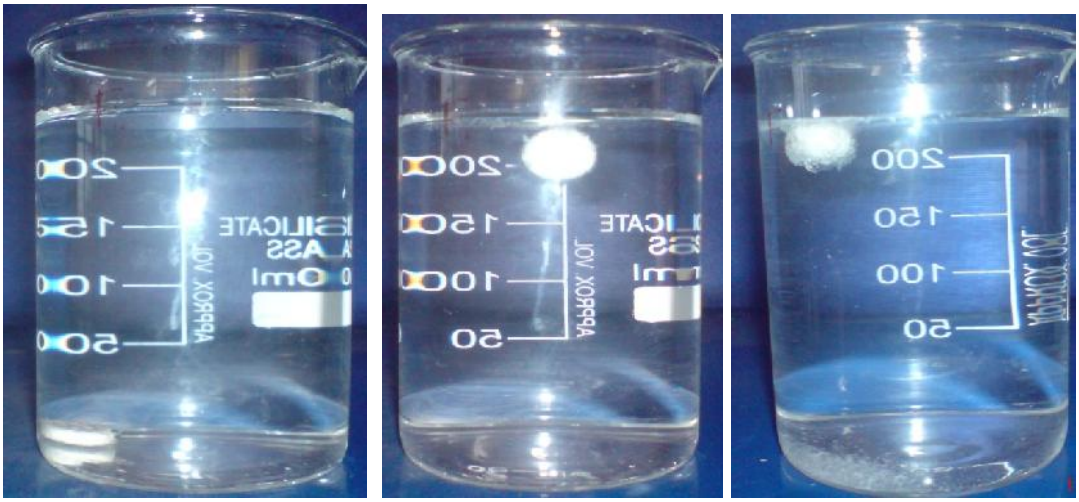
The tablets floated, while immersing in 0.1 N HCL solution PH(1.2) at 37^0C, and remained buoyant without disintegration. Table 20 showed the results of buoyancy study and shows buoyancy character of prepared tablet.

Table 20:Buoyancy and floating time

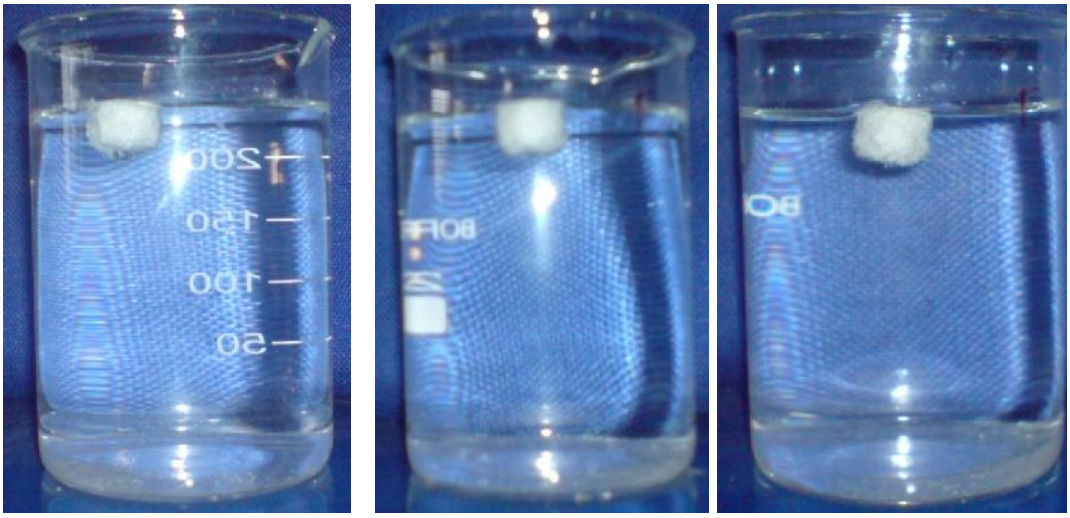
S.No	Batch No	Buoyancy lag time (sec)	Floating duration (hrs)
1	F_1	45	>12 hrs
2	F_2	60	>12 hrs
3	F_3	50	>12 hrs
4	F_4	45	>12 hrs
5	F_5	70	>12 hrs
6	F_6	90	>12 hrs
7	F_7	45	>12 hrs
8	F_8	50	>12 hrs
9	F_9	55	>12 hrs

Formulation F4 containing xanthan and guar gum showed good BLT of 45 sec,while the formulation containing xanthan gum alone and guar gum alone showed highest BLT and TFT of greater than 12 hrs. This may due to the amount of polymer and gas generating agent, which were kept constant in the present study . The gas generated cannot be entrapped inside the gelatinious layer, and it escaped leading to variation in BLT and TFT.

From the results it can be concluded that the batch containing both xanthan gum and guar gum showed good buoyancy lag time (BLT) and total floating time(TFT).



0 min **2 min** **4 hr**



8 hr **12 hr** **24 hr**

Fig No.18: *In vitro* buoyancy study of carvedilol floating

7.4.2 Swelling Index:

The percentage swelling obtained from the water uptake studies of the formulations was shown in Figure 19-21. The formulations with Xanthan and guar gum showed the swelling and tablet integrity. The change in sodium bicarbonate concentration did not show any effect on swelling of the tablet. Complete swelling was achieved at the end of 6 hr, then diffusion and erosion takes place. The formulation containing xanthan gum shows the higher swelling compared to that of the formulations containing both xanthan and guar gum and guar gum alone. The swelling index of the tablets increased with an increased in the polymer viscosity grades.

Table 21:% swelling index of formulated floating tablets

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
1hr	20.27	26.43	19.21	18.48	20.11	18.06	10.24	17.64	9.25
2hr	36.09	44.60	34.12	30.12	33.16	29.18	19.19	28.72	16.37
3hr	51.02	60.57	49.56	47.23	48.32	42.70	28.12	46.16	24.43
4hr	62.47	72.22	60.89	54.42	60.06	53.04	39.21	52.09	36.45
6hr	72.09	85.11	70.06	63.15	71.51	59.56	45.79	60.99	41.28

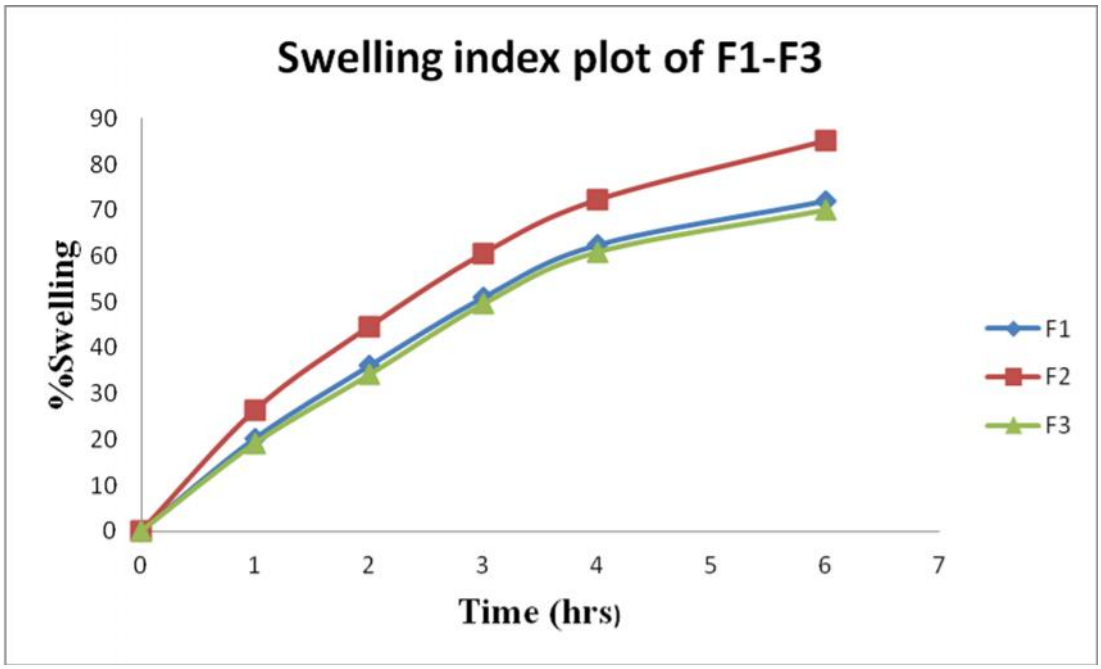


Fig No.19: Swelling index plot of F1-F3

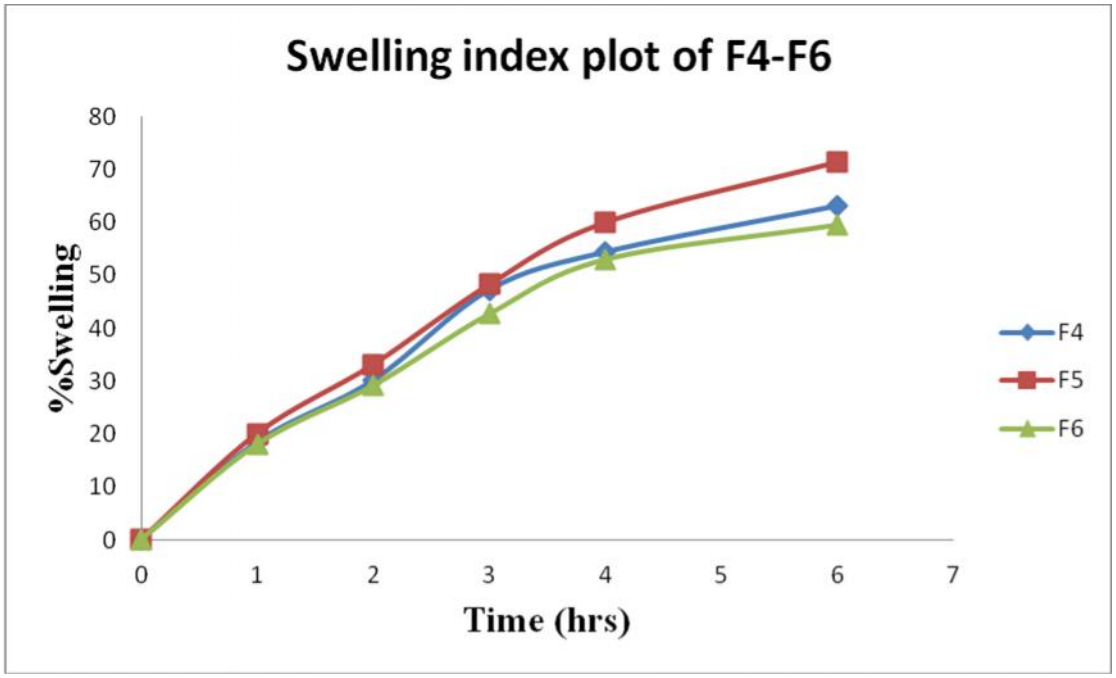


Fig No.20: Swelling index plot of F4-F6

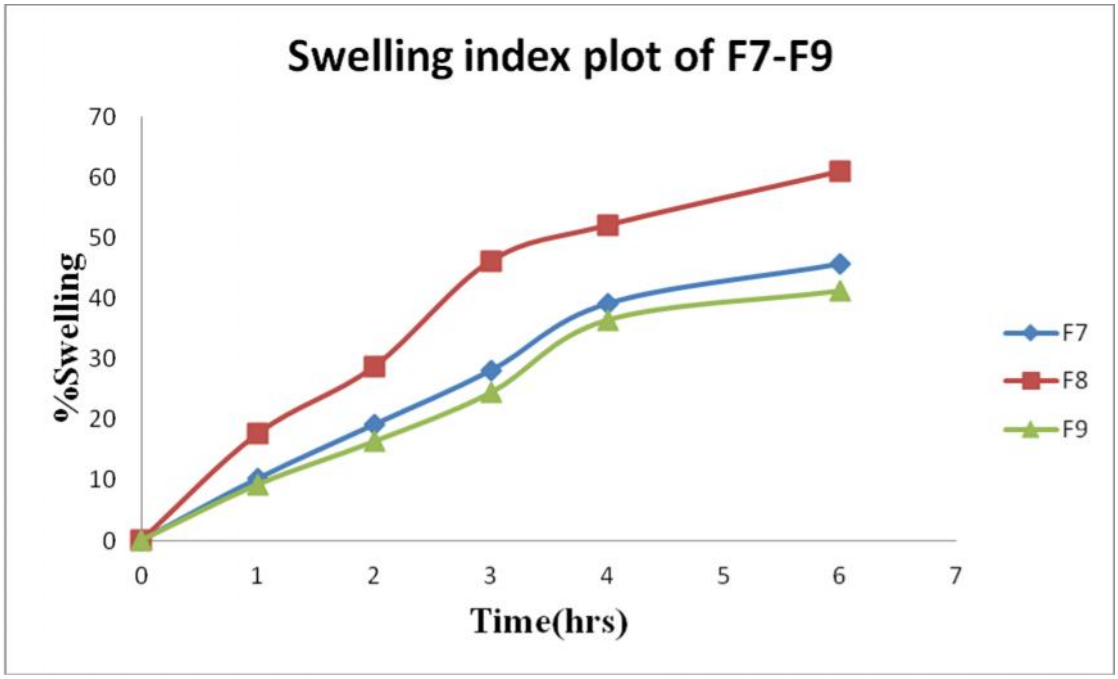


Fig No. 21:Swelling index plot of F7-F9

7.4.3 Invitro drug release study of formulated floating controlled release formulations

Dissolution study was carried out according to the procedure given in 6.5.8.The results was shown in fig no 22. Data for F1-F9 formulations given in table no 22.

Table 22: Invitro drug release study

TIME	CUMULATIVE PERCENTAGE DRUG RELEASE (%)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	15.68	21.98	20.18	10.23	20.16	9.31	8.14	15.27	8.00
2	26.22	44.03	31.77	14.76	31.52	13.16	11.56	25.32	10.02
3	37.04	60.07	41.91	17.86	39.23	16.56	15.12	36.59	14.56
4	48.09	72.17	52.76	21.97	50.36	20.96	17.56	45.62	16.23
5	55.71	79.46	58.82	26.53	56.51	25.43	22.16	50.06	20.58
6	62.05	85.18	63.11	31.65	61.68	30.62	26.28	54.42	24.12
7	69.16	92.71	67.99	38.15	66.79	36.25	34.47	58.69	30.16
8	76.96	99.51	72.34	44.87	71.24	40.17	37.52	63.16	34.19
10	88.34	-	81.19	56.01	80.11	50.21	44.75	70.28	39.78
12	99.11	-	90.76	70.03	89.16	58.75	49.89	78.44	43.65
14	-	-	94.42	77.36	92.14	63.23	52.13	83.59	47.57
16	-	-	99.85	84.06	99.58	70.11	56.14	90.16	52.18
20	-	-	-	97.02	-	76.51	62.78	99.31	56.24
24	-	-	-	99.64	-	82.09	66.25	-	60.12

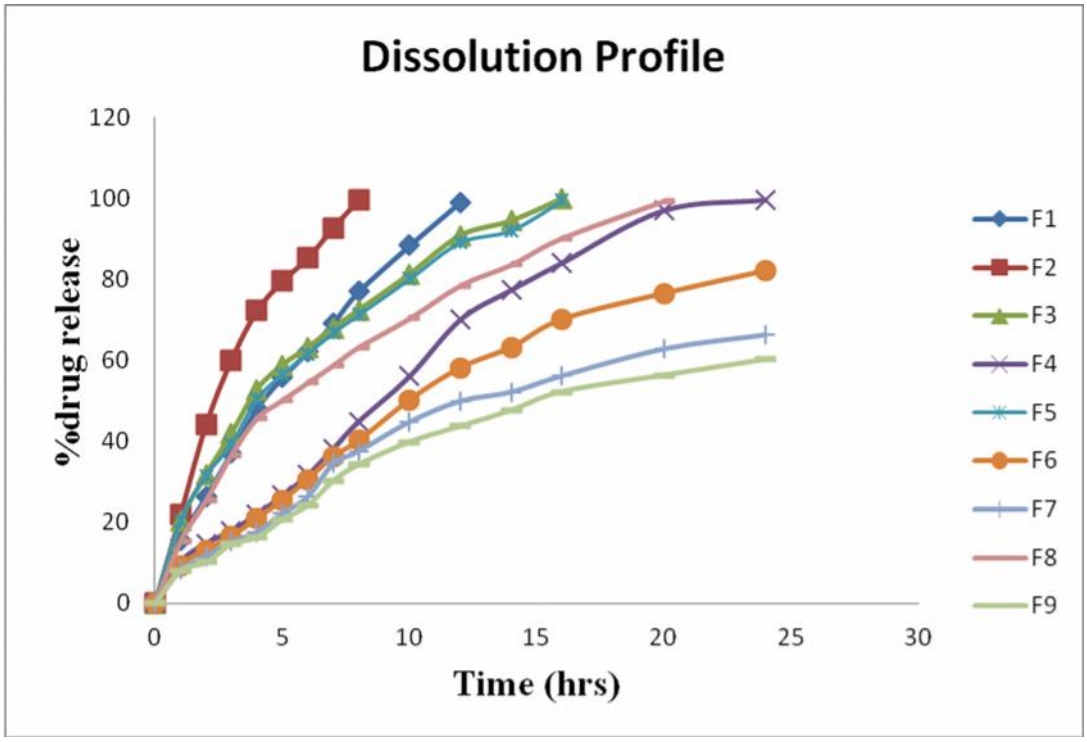


Fig No.22: Invitro drug release study

The formulated controlled release floating tablets were then subjected to *Invitro* dissolution test for evaluating drug release from the formulation. The Invitro dissolution test was carried out in 900 ml of 0.1 N HCL in USP-II paddle type apparatus at 50 rpm and 37±0.5^{o}C. The results of dissolution study was depends on polymer concentration. Formulation containing xanthan gum alone (F2,F5,F8) released fastly compared to that of guar gum alone (F3,F6,F9) due to the less binding nature and controlled release property. Formulation F4 containing Xanthan gum (10 mg) and guar gum (10 mg) had given drug release 99.76% in 24 hrs. Then the formulations containing Xanthan gum and guar gum were given better release profiles when compared with formulations containing xanthan gum alone (F2,F5,F8) and guar gum alone (F3,F6,F9).

7.5 KINETIC STUDIES OF FLOATING TABLETS OF CARVEDILOL:

Table-23: kinetic study of optimized formulation F4

Time (hrs)	Log Time	√Time	cumulative % drug release	Log cumulative % drug release	cumulative % drug remained	Log cumulative % drug remained
0	0	0	0	0	100	2.000
1	0	1.000	10.23	1.009	89.76	1.953
2	0.301	1.414	14.76	1.169	85.24	1.93
3	0.477	1.732	17.86	1.251	82.23	1.915
4	0.602	2.000	21.97	1.341	79.03	1.897
5	0.698	2.236	26.53	1.423	73.47	1.866
6	0.778	2.449	31.65	1.5	68.35	1.834
7	0.845	2.645	38.15	1.581	61.88	1.786
8	0.903	2.828	44.87	1.651	55.13	1.741
10	1.000	3.162	56.01	1.748	43.99	1.643
12	1.079	3.464	70.03	1.845	29.97	1.476
14	1.146	3.741	77.36	1.888	22.64	1.354
16	1.204	4.000	84.06	1.924	15.94	1.202
20	1.301	4.472	97.02	1.986	2.98	0.474
24	1.380	4.898	99.64	1.998	0.36	-0.443

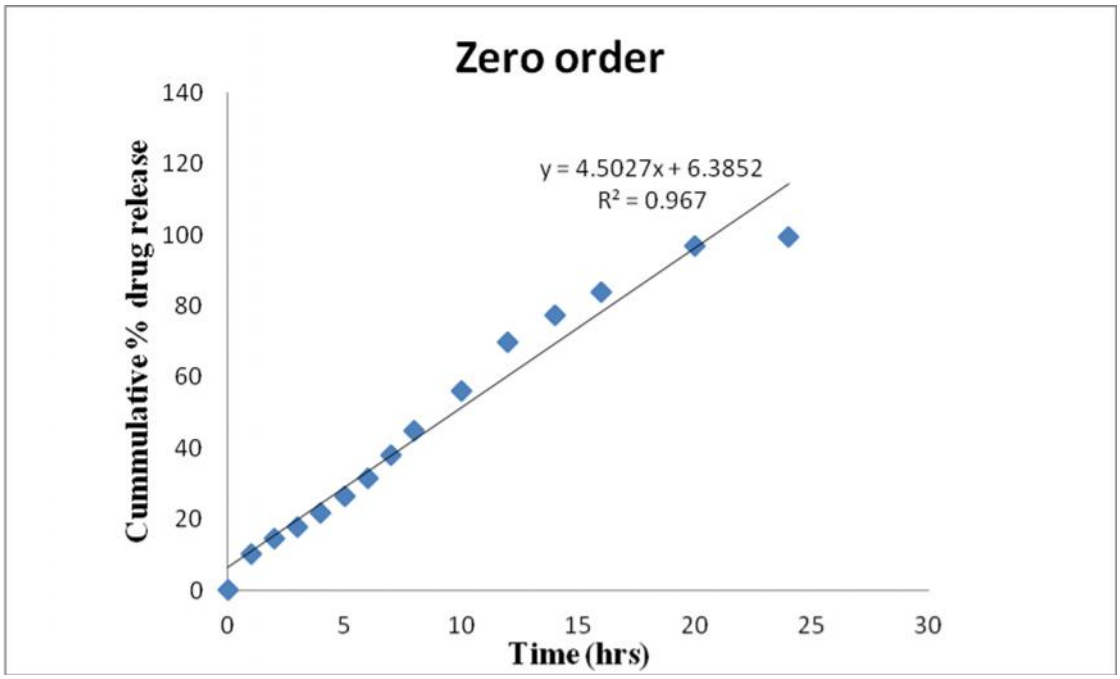


Fig No. 23: zero order plot

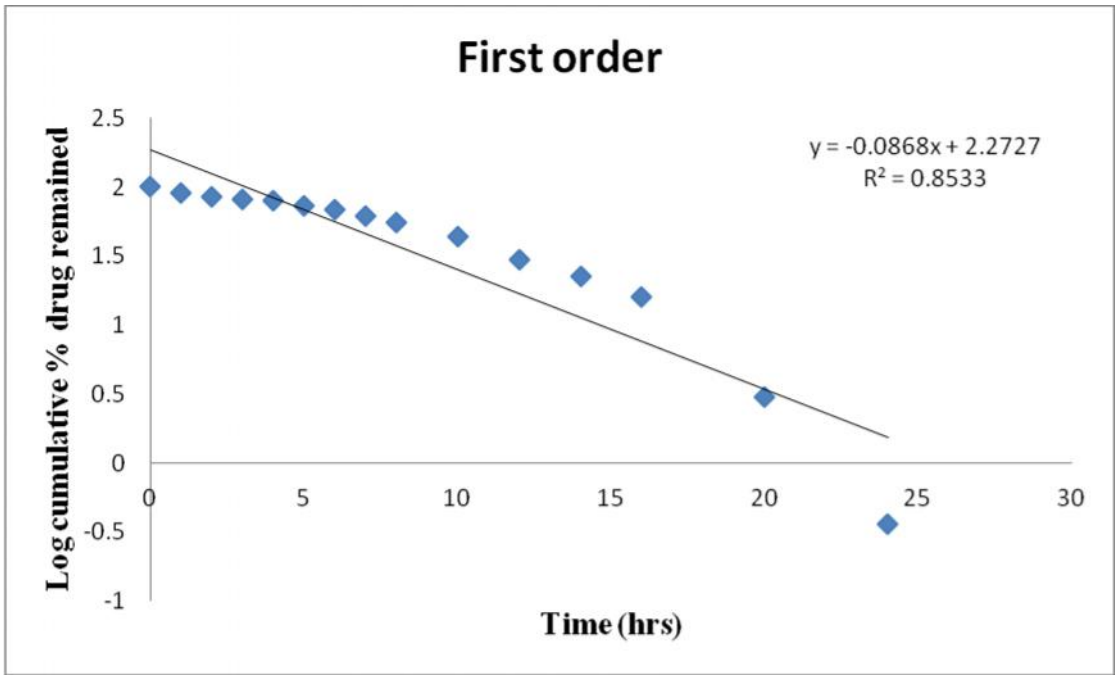


Fig No. 24: First order plot

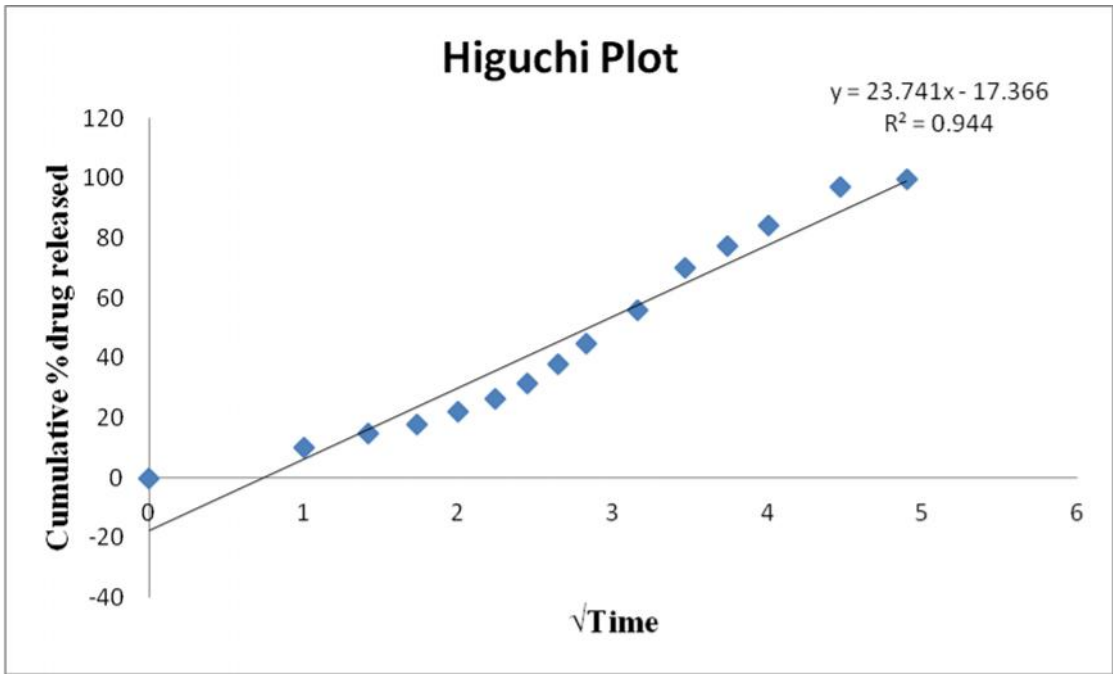


Fig No. 25: Higuchi plot

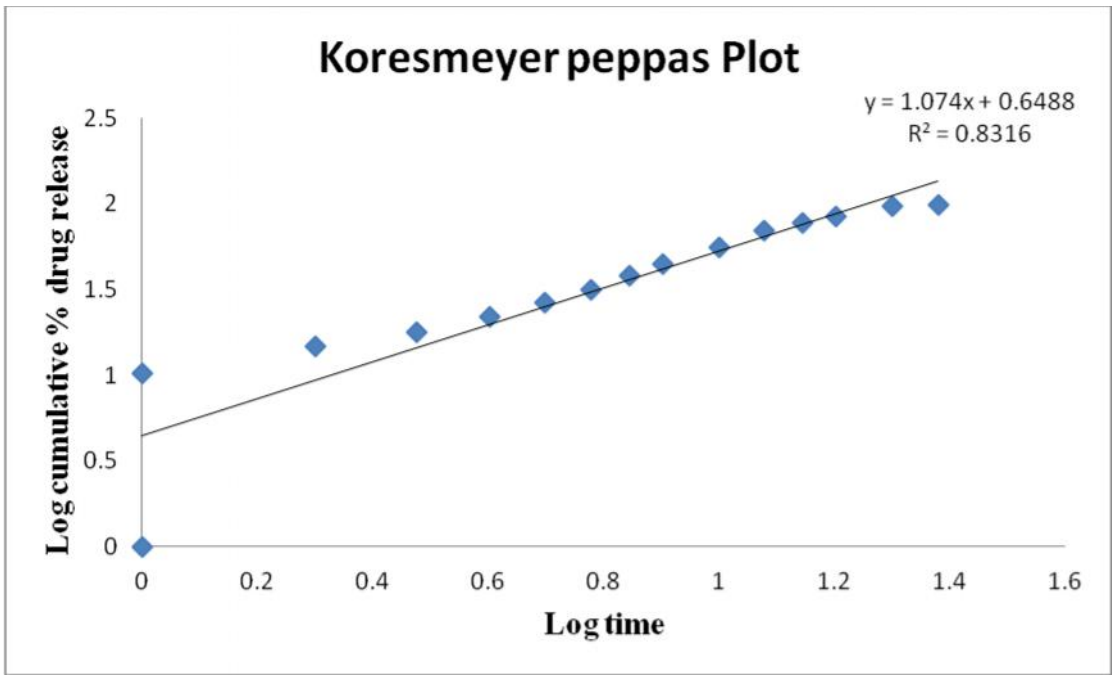


Fig No. 26: koresmeyer peppas plot

KINETICS OF DRUG RELEASE

Table-24:

Formulation	Regression coefficient of Zero order	Regression coefficient of First order	Order of release
F4	0.967	0.853	Zero order release

Table-25:

Formulation	Higuchi Model		Korsemeyer Peppas Model	
	SLOPE	**R^2**	**SLOPE**	**R^2**
F4	23.74	0.944	1.074	0.831

In order to determine the mechanism of drug release form the formulations , the *Invitro* dissolution data was fitted to Zero order, First order, Higuchi plot and Korsemeyer-peppa's plot was drawn and interpretation of release exponent value (n) was calculated and results are shown in tables 24-25; figs 23-26. The results of R^2 for zero and first order were obtained as 0.967, 0.853. Based on that we confirmed that the optimized formulation followed zero order release.

The drug release was diffusion controlled as the plot of optimized formulation F4 was found 0.944 as regression coefficient in higuchi plot. From korsemeyer peppa's plot the release exponent value n was found as 0.813 and it was confirmed as the release of drug from the formulation was founded as anomalous non-fickian transport of diffusion.

7.6 STABILITY STUDIES:

The optimized formulation was subjected to stability studies at $40^{o}C \pm 2^{o}C$ / 75% RH ± 5% for 3 month and analyzed weight variation, hardness, friability, drug content.

Table-26:

TEST	0 days	30 days	60 days	90 days
Weight variation	99±0.87	99±0.55	98±0.84	99±0.76
Hardness	4.5	4.4	4.4	4.3
Friability	0.68	0.69	0.69	0.70
Drug content	99.83±0.04	99.59±0.07	99.39±0.07	99.28±0.06

The results indicated that there was no change in weight variation, hardness, friability and drug content.

Dissolution data of stability for optimized formulation F4

Table-27: Dissolution data of stability for formulation F4

Time (hrs)	0 days	30 days	60 days	90 days
0	0	0	0	0
1	13.47	13.23	12.98	12.78
2	20.76	20.42	19.71	19.63
3	26.59	26.37	26.12	25.93
4	34.83	34.49	34.32	34.12
5	39.15	39.02	38.86	38.65
6	43.21	42.98	42.76	42.12
7	47.46	47.23	46.99	46.83
8	51.01	50.94	50.78	50.67
10	59.82	59.63	59.41	59.19
12	70.76	70.34	70.28	69.87
14	76.04	75.83	75.57	75.28
16	82.15	81.97	81.45	81.11
20	92.99	92.98	92.87	92.74
24	99.89	99.74	99.56	99.23

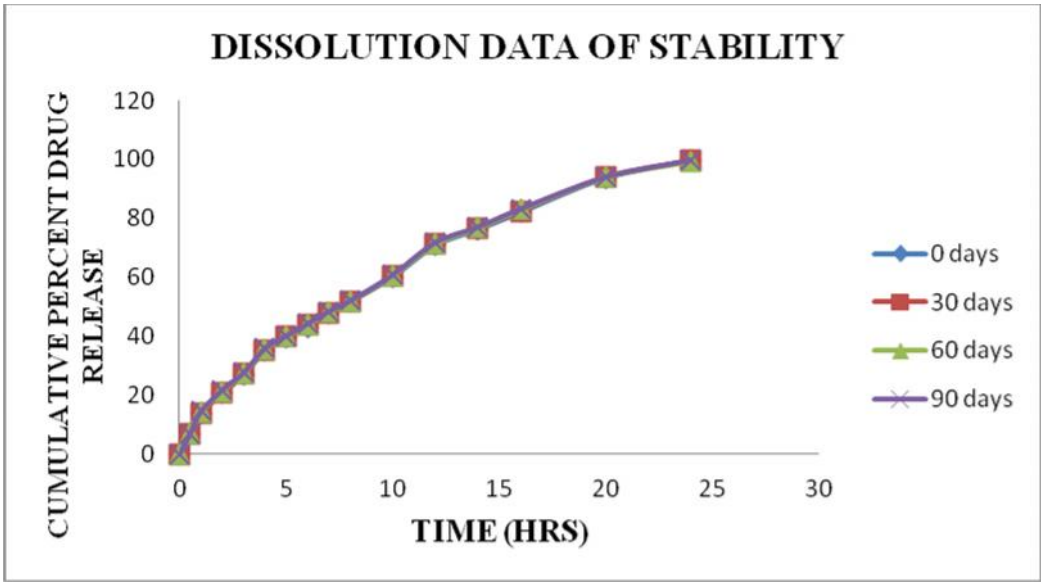


Fig. No. 27: Dissolution data of stability for formulation F4

The stability studies for optimized formulation F4 was carried out based accelerated stability conditions & study of various parameters carried out at 0, 30, 60, 90 days of intervals and the results found satisfactorily and that revealed that the optimized formulation was stable under accelerated condition.

Chapter VIII

Summary and Conclusion

8. SUMMARY AND CONCLUSION

The main objective of the present study was to develop floating controlled release formulation containing 20mg of carvedilol for once daily therapy by using natural polymers like xanthan and guargum. GRDDS improved the bioavailability and therapeutic efficiency of drug.

In the preformulation FTIR study was carried out for pure drug (carvedilol), carvedilol and excipients. It has not shown any interaction.Hence drugs were found to be compatible with excipients.

The formulations were prepared by direct compression method .The angle of repose values for formulations range from 26.04±0.03 to 29.01±0.07.Bulk and tapped densities were used for the measurement of compressibility index .The bulk and tapped values for formulations range from 0.260±0.01 to 0.347±0.04 and 0.320±0.03 to 0.391±0.07 respectively.The carr's index and hausner's ratio values for formulations range from 13.12±0.03 to 16.52±0.01 and 1.08 ±0.05 to 1.19±0.06 respectively. Thus all formulations exhibited good flow characteristics.

The prepared floating controlled release tablets were evaluated for various parameters like thickness, weight variation, hardness, friability and drug content uniformity. The thicknesses of tablets in all formulations were ranged from 1.2±0.16 to 1.3±0.53. The weight variations of tablets in all formulations were ranged from 99±0.02 to 101±0.06. The hardness and friability of all the formulations F1-F9 was found to be 4.2±0.73 to 4.5±0.28 and 0.45 to 0.83 respectively. Drug content of all the formulations were ranging from 98.76±0.19 to 100.92±0.21. The buoyancy lag time of all the formulations were ranging from 45sec to 90sec.

Compared to all formulations F4 showed the best buoyancy lag time, the buoyancy lag time for F4 was found to be 45sec.Total floating time of all formulations was found to be >12 hrs. The formulation containing xanthan gum shows the higher swelling compared to that of the formulations containing both xanthan and guar gum and guar gum alone.

The prepared tablets were then subjected to dissolution test for evaluating the *invitro* drug release .The dissolution studies were carried out in 0.1N Hcl in USP II appatarus at 37±0.5^{o}C. The results of the dissolution studies indicated that the polymer concentration was having a substantial effect on the drug release from the tablets .Formulation F4 gave better controlled drug release and floating properties in comparison to the other formulations .This formulation took 45sec to become buoyant.

The kinetic study was carried out for F4 formulation which showed that the drug release followed zero order kinetics followed by non-fickian diffusion.

The stability studies were carried out for F4 formulation at 45^{o}C /75% RH for 3months. Data revealed that there was no considerable difference.

From the above study , concluded that F4 was the optimized formulation which has shown better buoyancy time 45sec and drug release 99.88% in 24hrs. However, further invivo studies can be carried out to support the results.

Chapter IX

Bibilography

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